1961 REPORT
of the
SCIENTIFIC DIRECTOR

CLARENCE COOK LITTLE, Sc.D.

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TOBACCO INDUSTRY RESEARCH COMMITTEE

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Organization and Policy

The Tobacco Industry Research Committee is the sponsoring agency of a program of research into questions of tobacco use and health. It was organized in early 1954 by representatives of tobacco manufacturers, growers and warehousemen.

Soon after the T.I.R.C. invited doctors and scientists well known for their work in cancer and other diseases to serve on a Scientific Advisory Board to run a grants-in-aid program. This Board currently consists of nine scientists who maintain their respective institutional affiliations.

Grants by the Board through 1961 have been made to more than 120 scientists in over 80 hospitals, universities, and research institutions from funds that now total $5,450,000 appropriated by the T.I.R.C.

A list of research projects supported by the T.I.R.C. is included in this Report. Also included are abstracts of 60 research papers acknowledging support by the T.I.R.C. that have appeared in scientific journals since the 1960 Report and through December 1961. A total of 222 such papers have now been published by grant recipients.

The Scientific Advisory Board has full responsibility for research policy and programming. As a Board it does not directly engage in research for the T.I.R.C. and the T.I.R.C. itself does not operate any research facility.

Grants-in-aid for research are made by the Board to independent scientists who are assured complete scientific freedom in conducting their research. They alone are responsible for reporting or publishing their findings in the accepted scientific manner — through medical and scientific journals and societies.

From the outset the Tobacco Industry Research Committee has made clear that the object of its research program is to encourage scientific study for facts about tobacco use and health. Its position is that research will help provide the knowledge about lung cancer and heart disease for a full evaluation of all factors being studied in connection with these diseases.

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Executive Director

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East 42nd Street, New York 17, N. Y.

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Preface

A monograph on cancer morbidity*, issued by the United States Public Health Service, commented on statistical and epidemiological data as follows:

> "In the study of cancer, a disease that apparently can be induced by a multiplicity of etiological agents, one cannot realistically expect to do more than identify factors that appear to be frequently associated with cancer. The proof of an etiological relationship must then be sought through more intensive clinical or experimental studies."

This is substantially the position adopted in 1954 by the Scientific Advisory Board to the Tobacco Industry Research Committee. It was reaffirmed in 1960 and remains unchanged at the present time. It is a position that also is held by many others, including statisticians and researchers.

Evidence of Various Possible Factors

During this period significant evidence of various possible contributory causal factors in lung cancer has been accumulating from both statistical and experimental research.

Previous lung infections, air pollutants, genetic factors, stress, hormonal influences, viruses, diet, and other possible influences are being investigated further and, as they are, a more accurate perspective of the whole picture of lung cancer causation is emerging.

These factors are not cited either to answer or to evade the question as to what role, if any, tobacco may have in the origin of lung cancer. They do not and will not deter the Tobacco Industry Research Committee from continuing to support independent research which is trying to answer this question.

Lung Cancer Origin is Complex and Obscure

The present situation emphasizes the truth of what we and others have said repeatedly. The origin of lung cancer is complex and still obscure. There probably are many contributing factors.

However, development of research into various aspects of the lung cancer program has had to be carried on in an unusual and sometimes difficult psychological climate. This came about because there are those who would insist on accepting as a proved fact the hypothesis that cigarette smoking represents a primary causative factor in lung cancer. This group

*"Morbidity from cancer in the United States," Public Health Monograph No. 56, U. S. Department of Health, Education and Welfare, 1959, Washington, D. C. Page 4.

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makes one of the most definite and blunt designations of a specific cause that has been advanced for any major type of cancer, and they do so at a time when science is still trying to determine the basic origins of this disease.

Those who most actively promote this hypothesis have consistently ignored or, at best, have minimized the fact that numerous directly relevant experiments either have failed to support the hypothesis or have provided only weak or uncertain data.

This situation has tended to obscure the real nature of the problem and also the significance of research findings that are not consistent with preconceived attitudes toward tobacco .

Since its inception in 1954, the T.I.R.C. has advocated development of an accurate and objective perspective. This policy is reflected in the quality of the scientists who have been given research grants by the Scientific Advisory Board, in the kind of work they are doing, and in the scores of research reports they have published in the literature.

The complex nature of cancer origin is itself a delaying factor and no amount of enthusiasm for any one theory can either hasten or prevent the eventual detection and analysis of the various components and elements that are involved.

Trauma and Cancer

Another factor of importance in the general psychological climate that surrounds the lung cancer problem is the over-emphasis of the role attributed to irritation in the carcinogenic process. The matter is of great interest to the clinician.

The obvious trauma caused by x-ray burns or that resulting from the application of certain chemicals to the skin of laboratory animals is a striking phenomenon and quite naturally attracts the attention of the research worker or clinician.

It is well to remember, however, that any kind of obvious irritation *per se* is not necessarily or even usually a precursor to the essential intracellular change or changes that constitute what is called malignancy. If it were, it is probable that human beings would long ago have been wiped out by cancer.

In any trauma or area of irritation there are concentric rings or bands of tissue composed of the following types of cells:

(a) At the central point of the trauma, cells are killed and broken down. They cannot form cancer.

(b) Outside of these are damaged cells with impaired function and reduced power of cell division. These are not precursors of cancer.

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(c) Surrounding the whole affected area are normal cells entirely unaffected.

(d) *If cancer occurs, it is formed in the area which lies between (b) and (c). Here intact and visibly unharmed cells may be released from centralized control and actually may divide more rapidly than do the normal ones.*

In the process of uncontrolled and, up to now, uncontrollable growth that characterizes cancer formation, there may be observed changes in the number and morphology of the chromosomes. From time to time such changes have been considered to be of etiological significance.

Such changes are probably of little or no actual significance in cancer causation. There are many recorded observations of highly malignant tumors with the normal number of chromosomes. There are also many types of non-tumorous cells with striking abnormalities in number and/or conformation of the chromosomes.

Science must look *inside* the cell's most minute and delicate structures and must analyze and explain its finest and most intricate functions before the differences between the normal and malignant cell are understood.

Epidemiological Studies Not Enough

It is small wonder, therefore, that the data derived solely from epidemiological studies leave much to be desired as a foundation on which to base sweeping and dogmatic hypotheses of cancer causation. Scientists, physicians, and the public are recognizing that fact in ever increasing numbers, and are admitting the need of far more knowledge than we now possess before this complex problem is fully understood and the answers to its many challenges can be expected.

While the answers we seek are still not within our grasp, we now have a far better understanding of the questions. Clearly, progress is being made.

The findings of the past year, as reported by scientists throughout the country, indicate real hope for eventual solutions to the challenges of cancer, heart disease and other constitutional ailments.

I wish to express sincere thanks to my associates on the Scientific Advisory Board and to the associate scientific directors of the T.I.R.C., Dr. Robert C. Hockett and Dr. J. Morrison Brady. Dr. Hockett, who has been closely associated with the Board's research program for eight years, has made many valuable contributions to the review of research on the pages following. While this review illustrates the scope and complexities of problems being investigated, it is essentially optimistic and descriptive of genuine progress.

C. C. Little
Scientific Director

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The Progress of Research

Progress of the Tobacco Industry Research Committee program, as developed and carried out by the Scientific Advisory Board, is reflected only in part by the increasing number of papers published by recipients of grants. Since the 1960 Report, 60 new published papers have appeared, bringing the total to 222. Abstracts of the new published works are included in another section of this Report.

Mere numbers of papers, however, do not measure the significance of research progress. A review of completed and continuing research gives reason to believe that some of the year's developments open more direct paths toward discoveries that may be expected to contribute practical measures for coping with certain forms of cancer and cardiovascular diseases. This review essays to estimate the state of progress in several fields, to assess the impact of certain findings, and to define the nature of some unsolved problems.

The discussion is divided into these sections: I. Cancer Research. II. Human Lung Studies. III. Cardiovascular Studies. IV. Psycho-Physiological. V. Tobacco Chemistry and Biochemistry. VI. Other Studies.

I. *Cancer Research*

In planning cancer research it is helpful to distinguish two different levels of attack. A full and final solution of the cancer problem may be expected to come only when we understand the basic biological mechanisms of cell differentiation and of the regulation of metabolic and cell division processes. The most fundamental investigations of the day are at this level, and more effective participation in such long-range and basic research is definitely one goal of the T.I.R.C.'s program.

At the same time, research at a less basic level can be expected to produce useful information and sometimes to yield immediately applicable measures for partial control or delay of cancer in the human population. Many such measures have indeed been developed in the past.

Well-designed experiments at this level may be successful in appraising the relative effects of many controllable extrinsic, as well as intrinsic, factors upon the level of incidence of particular forms of cancer in animals. Perhaps the best hope of developing control measures for some forms of malignancy in the relatively near future lies in studies of this type. Scientific history provides many cases where such research not only solved immediate problems but also produced scientific by-products of even greater ultimate

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value. Pasteur's discovery of induced immunity may be traced to his original attack upon the practical problems of the beer and wine industries.

The Scientific Advisory Board, along with other scientists, has consistently held that pathogenesis of bronchogenic carcinoma must be a complex phenomenon and that real progress toward solution must be expected through discovery and relative evaluation of a whole series of contributory factors. This position has sometimes been misconstrued as implying that no progress in the control of lung cancer could be expected until the whole cancer problem could be finally and fully solved at the basic level of biological discovery. This is far from the true meaning of this position.

THE EXPERIMENTAL APPROACH

The several reports of statistical associations between cigarette smoking and lung cancer incidence made it logical to develop research to see if smoking could play a direct, primary role in the etiology of the disease. To be sure, statisticians worthy of respectful attention did point out many anomalies and inconsistencies in the statistical picture. Some even questioned seriously whether biases of several kinds might not invalidate the reported relationships. These legitimate questions about the statistics could, however, be left for eventual resolution by qualified experts in the field of epidemiology and statistics. The testing of the question concerning tobacco as a possible causative factor called for extensive experimental research in the laboratory and clinic.

Statistical Association Cannot Prove Causation

The point requiring re-emphasis is this: Even if a statistical association is assumed to be completely valid, it does not and cannot demonstrate that smoking is actually a factor in the etiology of human bronchogenic carcinoma.

It has been shown, for example, that there is an excellent correlation between socio-economic class levels and the incidence of "chronic bronchitis" in Britain. No clinician or statistician would suggest for a moment that the amount of money a man receives per annum could of itself cause any disease, unless he were actually infected by microbes from coins or paper money. We automatically proceed to consideration of such matters as dietary adequacy, housing conditions, kind of clothing worn, nature of employment, level of medical care, amount of rest or exercise, nature of recreation, exposure to the elements and other factors which may be *affected* by income and which in turn may influence incidence of the disease.

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The existence of a statistical association does not disclose the number of intermediate variables that may lie between the end result (disease) and the environmental factor orginally taken into account. The useful function of finding such a correlation thus lies in the clues and hints turned up which may be further and separately validated.

"Fallacy of Misplaced Concreteness"

In the particular illustration just given, the impossibility of a direct causal relationship is sufficiently obvious to prevent investigators from making premature or false inferences. In the case of the reported association between smoking and lung cancer, the statistical evidence is actually no different from that of the income-bronchitis situation and does not, of itself, permit any more reliable conclusion with respect to direct causation. Dr. Berkson has called this seizure upon the *apparently* obvious as an example of the "fallacy of misplaced concreteness."

A surmise that smoking could be a prime causative factor in lung cancer could be used only as a working *hypothesis* but not as a proved fact. Nevertheless, the habit of using this hypothesis from day to day as a generator of experimental designs seems to have induced some scientists to forget its wholly tentative status.

Even as an hypothesis, it actually contained a very serious limitation: Only a very small proportion of even the heaviest smokers ever develops this disease and it also occurs among nonsmokers. This is actually strong evidence that the etiology of the disease is complex and that a number of influences must act in concert in its genesis. The implication is strong that there must be factors determining the degree of susceptibility or resistance in individuals.

It would appear to be a promising enterprise to determine what these factors are, with the view of utilizing them in control of cancer. Yet this possibility has been largely ignored in practice. The relatively low incidence of lung cancer in heavy smokers as well as in the general population has been attributed rather pre-emptorily to "natural differences in susceptibility," as if these were unimportant or inaccessible to study. Gilliam's recent observation of the diminishing rate of increase in lung cancer incidence suggests the gradual disappearance of a particularly susceptible population.

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Animal Inhalation Tests Consistently Negative

One way used to study the hypothesis that cigarette smoke might be a prime causative factor in the genesis of lung cancer was animal experimentation. The most directly pertinent of these experiments were the numerous studies in which animals of several species were made to inhale fresh, whole cigarette smoke at frequent intervals over long periods of time, often during the whole natural span of life after weaning. These experiments consistently failed to produce squamous cell carcinomas of the type that are most prevalent in humans.

These failures, in view of the number, extent and duration of the tests by many able and experienced investigators, militated against the surmise that tobacco smoke could be a primary factor in the induction of such cancers. However, the problem of species differences in susceptibility could be raised, and general ignorance of the effects even of strong carcinogenic agents on the lung tissues left the reasons for negative results uncertain. Further work has helped clear up the uncertainties.

It was logical to extend these studies to investigations in which animals were made to inhale aerosols or fumes of potent, known carcinogens, including methylcholanthrene and 3,4-benzyprene. Such experiments on rats by Kuschner were also negative. Again, the results could be interpreted in several ways. The efficient lung cleansing mechanisms (including mucus flow, phagocytic activity, and absorption, metabolism and excretion) of the healthy animal might not permit a contact time, or effective dosage, adequate for carcinogenic action.

The problem of species differences in susceptibility could perhaps still be raised, though Andervont had long before shown that squamous lung carcinomas could be induced in C-57 black mice by transfixing threads impregnated with 1,2,5,6-dibenzanthracene through the lung. This had demonstrated that mouse lung cells are biologically capable of transformation into malignant tissue of this histological type.

Rigdon and Shubik have shown that large doses of carcinogenic hydrocarbons introduced into the tracheas of ducks and hamsters respectively in oil solutions will produce cancers of various types. Similar experiments using tobacco smoke condensates have failed to produce cancer. These experiments have, however, further confirmed the fact that lungs of several animal species are biologically susceptible to malignant change when dosages of known carcinogens are sufficient and contact time is long enough.

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Trauma and Regeneration Possibly Involved

Andervont's studies and their extension by Kuschner using thread transfixion introduced the additional factor of trauma along with increased contact time and interference with normal cleansing mechanisms. The relatively high incidence of squamous cell carcinomas in these experiments drew attention to the possible role of trauma and perhaps of attempted regeneration in susceptibility of the lung to carcinogenesis.

Subsequently, a series of studies showed that a number of radioactive and potent chemical substances can induce epidermoid lung cancers in rats and mice. These studies are not directly illuminating with respect to the etiology of epidermoid lung cancer in man, because they were carried out on animals and they employed very powerful agents not widely encountered by human beings in ordinary life. The studies do, however, dispel any doubts about lack of species susceptibility.

Meanwhile, clinical and epidemiological studies of human subjects by a number of investigators pointed toward the possibility that damage to the lung, followed by regeneration, might be a predisposing factor in human lung cancer, whether the damage was due to tuberculosis lesions, infarction, or mechanical injury.

Winternitz long ago pointed out the frequent occurrence of severe metaplasias in the lungs of persons who died following influenza in the 1918-19 epidemic and had called attention to their "precancerous appearance." Several investigators had attempted to produce lung cancers in animals by repeated influenza infections but, though metaplastic changes were produced, no truly invasive tumors developed.

Cancer Experiments with Viruses

By combining repeated influenza infections with inhalation of synthetic smog, Wiseley, Kotin, Fowler and Trividi have obtained invasive and metastatic squamous cell carcinomas in the lungs of C-57 black mice at a substantial level of incidence. Almost at the same time, Martin and his collaborators showed a synergistic action between several viruses and a specific chemical carcinogen by obtaining tumors when combined small doses of virus and chemicals were given. Given separately, at the same levels, these agents failed to induce cancer.

Stanton also has reported the induction of squamous cell lung carcinomas by chemical carcinogens administered intravenously into rats in which areas of lung infarction had been produced.

These recent events are cited to illustrate the rapid development of methods for study of squamous cell carcinoma in animal lungs.

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These methods provide a basis for evaluating the relative effects of many other extrinsic and intrinsic factors on the rate and level of incidence of bronchogenic carcinoma in animals. By suitable design, it should become possible to evaluate the effects of age, sex, nutritional status, excess or deficiency of hormones, stimulation or depression of the reticuloendothelial system, cancer promoting agents, various types of trauma, irritants, mucus composition and abundance, activity of cilia, efficiency of detoxification mechanisms and many other factors.

Tests Continue on Tobacco Smoke

Tests of tobacco smoke in this experimental biological system have not yet been completed. So far, the indications from these and many other tests of the activity of tobacco smoke, are that the smoke is much too feeble to play a role in the etiology of lung cancer as a direct contact carcinogen. This does not necessarily exclude tobacco from having any role at all, nor is any such role established. More investigations are necessary on the suggestions of possible indirect, contributory roles for tobacco.

As the experimental systems described gradually permit the relative evaluation of all the possible external and internal influences listed above, it should become possible to determine whether and to what extent tobacco smoke can contribute, whether as irritant, promoter, modifier of ciliary activity, influencer of nutrition or by any other means. It is a task of considerable magnitude, but the means now seem to be at hand.

The fortunate aspect is that, as the contributions of the various suspect factors are evaluated, methods of nullifying or blocking some of them may become apparent. Of course, the problems of species differences and relevance to man will remain to be resolved. Hopefully, effective methods of reducing the toll of human lung cancer may become evident from this type of work.

CURRENT CONTRIBUTIONS FROM T.I.R.C. PROGRAM

The program of cancer research supported by T.I.R.C. grants produced several significant developments during the year.

The suggestion that some transmissible agent is produced by certain tumors has come from further study of the increased concentrations of deoxyribonucleic acid (DNA) in tumor-bearing rats in tissues distant from the actual tumor. Extracts of lung, kidney, liver and spleen of rats bearing the Walker 256 carcinoma and the Jensen sarcoma have been found to incorporate thymidine-H^3 more rapidly than those from normal rats, indicating a possible influence from the tumors.

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In three different laboratories, exposure of cultured cells to smoke and non-smoke gases was studied with description of morphological changes, alterations in growth rates, and modification of modal values of chromosome numbers.

Effects of irradiating human amnion cells have been similarily described. Since morphological changes and ploidy of chromosome constitution are not simply or directly diagnostic of malignant modification, it is expected that future studies at the cell and tissue culture levels under T.I.R.C. support will place increasing emphasis on changes in the dynamics of the living cell.

Further quantitative cytochemical studies on the relation of DNA to various pathological conditions also point toward the conclusion that deviations from normal in amount and distribution of DNA are not specifically diagnostic of malignant transformation, but rather of growth or regeneration regardless of cause, or of DNA virus infection.

No Lung Cancers in Mice Exposed to Smoke

A new summary reviewed the histological, cytological and cytochemical study of the tracheobronchial tree and lungs of mice exposed to cigarette smoke. It confirmed the previously reported variability of response, ranging from absence of significant histological change, through mild bronchitis with swollen epithelium and mild hyperplasia, to severe bronchitis with a typical basal cell hyperplasia, squamous cell metaplasia and occasional dysplasia or "carcinoma-in-situ." Invasive carcinoma was *not* found. The extreme variability of response, regardless of dose and duration of exposure, pointed to contributing factors, such as latent virus infections, characteristic of the individual animal.

Long-continued studies with the white Pekin duck have culminated in production of non-metastatic neoplasms of varied type in the lungs of birds given methylcholanthrene in polysorbate 80 by intratracheal infusion. Tobacco smoke condensates similarly infused have not produced tumors.

BIOASSAY METHODS

Numerous studies have been supported by grants in the effort to obtain a more exact quantitative method of testing for relative over-all "carcinogenic potencies" of various substances and mixtures, including tobacco smoke and condensates.

On a strictly theoretical basis, "carcinogenic potency" is not an inherent property of a chemical substance. Rather it is the result of an interaction of some kind between an agent and a dynamic living entity —

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the host. "Relative potency," therefore, implies comparison of activity within some fixed or standardized biological system. Each such system will produce its own scale, since there are wide variations in reaction both among and within species.

If several scales based on different biological phenomena, other than actual tumor production, are set up, there is no guarantee that any parallelism will exist between them in the relative positions assumed by the various agents tested. If a degree of parallelism should occur among several such scales, it might encourage confidence in their significance, especially if one at least is based on actual tumor production.

Obviously a method more rapid and controllable than mouse skin painting, and requiring only very small quantities of test substance, would be of great practical value in speeding research.

In the T. I. R. C. grant program over the past half dozen years, a score of methods have been tried out in the attempt to test for the relative "carcinogenic potency" of tobacco smoke and other substances. Such information would, it was thought, help assess the hypothesis that such smoke contributes to human cancer as a contact carcinogen and help determine where emphasis in research should be directed. None of these earlier attempts proved to be satisfactory for relative quantitative evaluation. Most, but not all, gave completely negative results. But even though not wholly satisfactory, these many studies produced an overall impression that tobacco smoke of normal character, in its tenuous state, is too weak a carcinogen, if it is one at all for humans, to act in this capacity as a generator of human lung cancer.

Encouraging Results in Three Areas

Now the benefits of this work are coming to fruition. The research for more satisfactory bioassay methods has entered a new phase which appears encouraging along three lines:

1. A method based on the activity of "carcinogenic agents" in enhancing growth of transplanted tumor and normal skin grafts has been shown capable of quantitation, and an "activity scale" for a large series of highly purified polycyclic hydrocarbons is in construction.

2. Further standardization is in progress for a protozoan assay for carcinogenic hydrocarbons, based on the response of *Paramecium caudatum* to ultraviolet and related radiation following exposure to the hydrocarbons in high dilution. A second potency scale is also to be constructed by this method, with use of the same samples of highly purified hydrocarbons.

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3. A third projected scale is to be based upon animal skin tumor production by an accelerated method, if plans materialize. The relative evaluation of various "unknown" substances on these scales is contemplated in due course, when background information becomes adequate.

Conference on Bioassay and Carcinogenesis

Many of the matters outlined above were discussed in a round table conference on May 25, 1961, in the offices of the Committee.

Besides members of the Scientific Advisory Board and staff, the following guest scientists participated:

DR. T. D. DAY, University of Leeds School of Medicine, Leeds, England

DR. WALTER E. HESTON, National Cancer Institute, Bethesda, Md.

DR. FREDDY HOMBURGER, Bio-Research Institute, Inc., Cambridge, Mass.

DR. ROBERT W. HULL, Northwestern University, Evanston, Ill.

DR. CHARLES J. KENSLER, Arthur D. Little, Inc., Cambridge, Mass.

DR. WILLIAM E. POEL, University of Pittsburgh, Pittsburgh, Pa.

DR. MURRAY J. SHEAR, National Cancer Institute, Bethesda, Md.

DR. CONSTANTINE S. STEPHANO, Stephano Brothers, Inc., Philadelphia, Pa.

DR. HAROLD STEWART, National Institutes of Health, Bethesda, Md.

MR. G. F. TODD, Tobacco Manufacturers' Standing Committee, London, England.

II. *Human Lung Studies*

Among studies on pulmonary function and physiology was a significant contribution in the measurement of "airway resistance" by the method of body plethysmography. Inhalation of cigarette smoke both by normal persons and patients with various lung diseases, whether habitual smokers or nonsmokers, produced a mild bronchoconstriction lasting from 10 to 80 minutes in most individuals. The effect did not appear to mediate through nicotine or other volatile substances and could be prevented by isoproterenol. Data were inadequate to warrant relating of this effect causally to initiation or aggravation of chronic pulmonary disease.

A review has appeared describing experience in the cooperative study of pathological anatomy of the human bronchial tree and lungs which the

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Scientific Advisory Board initiated in 1954. About 3,000 cases were investigated, yielding 8,590 slides from males and 3,661 from females. Participating were 12 pathologists in different locations around the country. The review reports chiefly on problems of diagnosis and classification. The study is now being extended under auspices of the United States Public Health Service.

A more detailed report by one of the participants in the cooperative study has indicated that only 48 percent of the cases could be considered normal and fewer of these occurred among smokers than among nonsmokers. Results of such studies indicate the many problems in defining pathological changes and interpreting their significance.

III. *Cardiovascular Studies*

Several of the cardiovascular diseases have been reported by investigators in epidemiology to be associated with the use of tobacco, especially cigarettes. As in the case of the other association, these reports have given impetus to additional studies on the epidemiological level as well as to many of a clinical or experimental nature. The object has been to determine whether the associations are truly meaningful and whether they reflect any contribution by smoking to the etiology of these diseases, or whether the link with smoking is only fortuitous or indirect, through intermediate common factors.

Many Other Factors Also Being Studied

Among other factors under investigation in studies of cardiovascular disease development are heredity, emotional constitution, stress and the individual manner of reacting to stress, physical activity in relation to caloric intake, relative body weight, metabolic characteristics, thyroid activity and dietary habits, especially with respect to the amount and kinds of fat consumed. Sex and ethnic origin are also involved.

Recent progress in several centers suggests that a distinction may need to be drawn between those influences that affect the rate of progression of chronic vascular degenerative processes such as atherosclerosis, and those that may help precipitate acute episodes such as myocardial infarction, the mechanisms of which still elude full elucidation.

Evidence emerging from the Tobacco Industry Research Committee program and elsewhere suggests that the prevalent types of chronic vascular degeneration are not significantly influenced in rate or degree by the periodic administration of nicotine in small amounts over a long period or by the moderate practice of smoking by average persons. Still obscure are

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the mechanisms that precipitate an acute episode in persons with advanced underlying vascular disease, who are consequently more vulnerable to all kinds of stress.

Efforts to solve these problems at the epidemiological level are fraught with many difficulties. Presumably the degree of vascular degeneration in human beings can be accurately determined only at autopsy by anatomic methods. Though accidental deaths constantly provide samples which cut across all lines of age, sex and race, the problem of acquiring the needed data on life habits of these victims, by retrospective methods, is formidable. Prospective studies, while permitting better access to information about personality, diet, smoking, body build and the like, do not conduce to acquisition of anatomic information in a universal or non-selective, random manner and thus depend upon vaguer clinical indications of cardiovascular pathology. They must, moreover, for practical reasons, use populations confined to the older age groups.

Human Arteries Are Examined

Despite difficulties, a pathologic-anatomic study of human arteries, recovered from accident victims, is being supported. Persistent and ingenious efforts are made to acquire and validate as much data as possible, retrospectively, about the pertinent characteristics and life-habits of the subjects.

To compare approaches, techniques and findings in this field, a conference was held during the year to which scientists involved in studies involving similar techniques and problems were brought together.

Conference on Atherosclerosis Studies

This conference was held in the offices of the Tobacco Industry Research Committee on May 26, 1961. In addition to staff and members of the Scientific Advisory Board, the following investigators participated.

DR. WILLIAM G. BEADENKOPF, New York State Department of Health, Albany, N. Y.

DR. THOMAS R. DAWBER, U. S. Public Health Service, Framingham, Mass.

DR. IRA GORE, Veterans Administration Hospital, West Roxbury, Mass., and Harvard Medical School

DR. GLORIA GALLO and DR. MICHAEL LYONS, New York University College of Medicine, New York City

DR. HENRY C. McGILL, JR., and MRS. MYRA L. RICHARDS, Louisiana State University School of Medicine, New Orleans, La.

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Progress in Studies of Tobacco Effects

An epidemiological study on a large population of living male subjects, including many measurements and functional tests, provided no evidence of large or important differences in circulatory activity between groups of habitual smokers and nonsmokers. There was little evidence of deterioration of cardiovascular "fitness" in smokers performing work tests. Heavy smokers had consistently lower relative body weight, and higher basal oxygen consumption. Differences in resting blood pressures were either nonsignificant or tended to be lower among smokers.

Because of reported differences in the relative incidence of ischemic heart disease among the three major ethnic groups of South Africa, a study was made among 600 healthy representatives of these groups. Consideration was given to smoking habits, income, occupation, diet, anthropometric measurements, arterial pressures, and total blood cholesterol levels, as well as distribution of this lipid between alpha-and beta-lipoprotein. No significant relationship was found between smoking and age, income, nature of occupation, height, weight or degree of obesity. A highly consistent difference was found in the distribution of cholesterol between the alpha-and beta-lipoprotein fractions, however, and these differences were paralleled by differences in the customary dietary fat intake. It was therefore proposed that smoking may exercise an indirect influence by modifying the selection of foods through effects on the taste sense. Subsidiary studies provided some preliminary evidence that smokers may prefer salty, spiced and high-fat foods and may experience a diminished sensitivity to bitter taste.

In a long-term prospective study designed to elucidate the precursors of hypertension and coronary disease, it has been reported that white male medical students who are the offspring of two parents affected with these diseases, are significantly different from the offspring of two unaffected parents. On the average, the sons of the affected parents are 10 pounds heavier, more frequently have hypercholesteremia, show higher resting systolic blood pressure levels and are more likely to be smokers. While these differences are not great, they are compatible with the hypothesis of multifactorial inheritance. These observations recall the possibility that smoking habits may reflect pre-existing constitutional factors, rather than necessarily contributing causally to producing the differences.

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Study of Serum Free Fatty Acids

The observation, from animal studies, that nicotine may release epinephrine and norepinephrine from depots and thus indirectly trigger the mobilization of free fatty acids (FFA) into the circulation from tissue fat deposits, prompted a similar study in a limited number of human subjects. The smoking of two cigarettes was found to produce an elevation in serum free fatty acids. The response was not related to age, sex, general smoking habits, type of cigarette or pre-smoking level of FFA. Total cholesterol was not affected. Non-smoking controls subjected to otherwise identical procedures also experienced a moderate but smaller increase in FFA.

Such mobilization of FFA was to have been expected as a normal part of the response to any stress on the sympathetic nervous system. As such, it requires quantitative evaluation in relation to the effects of all other forms of stress to determine whether such effects are of any real significance in the atherosclerotic processes.

Meanwhile, a different group of investigators has shown that in the postabsorptive state, the human as well as the dog heart extracts a consistently higher percentage of free oleic acid than of any other free fatty acid present in arterial blood. It had been demonstrated previously that energy production of the heart depends largely on fatty acid metabolism.

Animal studies of vascular pathology, though much more easily controlled, are impeded by problems of species differences and difficulties of interpretation and application to human beings. However, further studies have been completed with rabbits fed cholesterol and cottonseed oil, nicotine, or a combination of all three, in comparison with controls.

A previous study had reported an apparently synergistic effect of nicotine in speeding and intensifying the production of peripheral circulatory changes and cardiac damage, with necrosis, by the atherogenic diet.

In the present experiment, however, the peripheral circulatory changes were minimal and cardiac necrosis absent. Since ergonovine had been used previously for tests to assess cardiac functional status, it was added to the regimen, and the necrotic conditions were again obtained. These necrotic effects are now attributed by the investigators to the additional action of ergonovine in the combination. Effects formerly considered attributable to the cholesterol diet, with or without nicotine, have diminished accordingly.

Response to Cigarette Smoking by Coronary Patients

The myocardial response to cigarette smoking in patients with coronary disease has been measured by catheterization techniques. Previous studies

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had shown that smoking enhances myocardial blood flow in normal subjects. Heart rate was accelerated in both groups by smoking and arterial pressure generally rose, but these changes tended to be more pronounced in the coronary group. A uniform increment of left ventricular work was also more pronounced in the latter. Myocardial oxygen usage was virtually unchanged. The coronary subjects did not experience increased myocardial blood flow during smoking, perhaps on account of the "fixed coronary resistance" alleged to exist in such patients. There was no evidence of myocardial ischemia during smoking, however, even in the coronary group.

A study of Buerger's disease among young men in the Orient produced evidence that this disease is distinct from the atherosclerosis or embolism of the peripheral vasculature that occurs more commonly in the United States, and where actual existence of a distinct Buerger's syndrome has been questioned. While all the 62 patients observed were smokers, the study suggested that the etiology and pathogenesis of the condition are probably complicated. Whether the essential lesion is truly an angiitis remains to be proved.

Pipe and cigar smoking have been shown to produce circulatory effects (a drop in skin temperature, increase in pulse rate and blood pressure) similar to but less marked than those found following cigarette smoking or tobacco chewing. Ballistocardiographic changes were less than those following chewing, but greater than those following cigarettes.

In an effort to throw light on the physiology of relative hyperreactivity to smoking by certain healthy young adults, in terms of blood pressure, heart rate, or cardiac output, the effects of preliminary small intravenous doses of hexamethonium, mephentermine or of a salt-solution placebo were studied. Individual differences in homeostasis were revealed but the changes were not readily grouped and the results were too varied for simple classification of subjects.

Fundamental Studies of Cardiovascular System

Numerous contributions to study of the cardiovascular system along fundamental lines were made during the year by recipients of Tobacco Industry Research Committee support without immediate bearing upon the effects of nicotine or smoking. Others contributed new or improved techniques for study of this system.

A notable series of such papers centered around the metabolic activities of the heart muscle under various conditions and influences and of the relations between biochemical events and drug actions, and the resulting mechanical and other functions. Others dealt with the rationale

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of treatments as based upon biochemical considerations, and with methods of measuring coronary blood flow and of assessing coronary artery insufficiency.

A beginning has also been made at the culture of normal rabbits' aortic and myocardial cells *in vitro*. Various nutrient media have been tested and the relative growth potentials of several cell types determined. Objectives are to observe metabolic activities as they may be affected by various extraneous substances, including nicotine.

These contributions are important scientifically to the further study of cardiovascular diseases and abstracts of all such papers are included in this report.

IV. *Psycho-Physiological Studies*

The general objectives of research in this field have been discussed in previous reports, and a continuing program is in the process of expansion.

Current reports include a study of relationships between constitution and other characteristics and smoking in a group of subjects all of Italian family origins from the area near Naples. Lean men were found to smoke more than stout ones, but the diets were not significantly different. Slightly higher serum cholesterol was found among smokers, but significant differences were not observed between smokers and nonsmokers in anthropometric measurement, in physical activity or in alcohol consumption.

An analysis of the smoking practices of a group of Harvard men in comparison with those of the general population has also appeared, as a by-product of a more intensive study of smoking as related to body build.

V. *Tobacco Chemistry and Biochemistry*

A series of studies on mechanisms of biosynthesis of *Nicotiana* alkaloids has reached publication as culmination of a long-continued program of study. Mechanisms of mammalian and bacterial metabolism of nicotine and related alkaloids have been traced through additional stages with full identification of intermediates by exacting methods. Several new constituents of tobacco have been identified.

Several years ago the question was raised whether the former use of arsenical insecticides might have contaminated the soils of tobacco growing areas with consequent long-sustained increase in arsenic absorption by tobacco plants. A three-year study of this subject, reported previously, showed that such soil contamination has not occurred to any significant degree. A new report on methodology of semi-micro analysis for arsenic in plant material and in soils, now published, will facilitate any future studies of this nature.

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VI. *Other Studies*

Other studies include reports from the continuing investigation of nicotine pharmacology which emphasizes especially effects upon the central nervous system with an ultimate view to elucidating some of the bases for the use of tobacco by humans in the context of life situations.

Tobacco use has been found to have no influence on the occurrence of episodes in so-called "periodic" disease.

A notable event in 1961 was publication of the comprehensive monograph, *Tobacco, Experimental and Clinical Studies*, by Drs. Larson, Haag and Silvette of the Medical College of Virginia. This 800-page book, whose completion was assisted by the Committee, should greatly increase the accessibility of scientific literature in the field and thus stimulate and facilitate new research, while contributing significantly to the development of better perspectives. The book is a comprehensive account of the world literature, based on study of more than 6,000 articles published in about 1,200 journals. It has been widely and favorably reviewed.

Other comprehensive reviews of the literature on the effects of tobacco on specific organs or systems appeared during the year. The literature on lung cancer from 1930 to 1960, was reviewed by Rigdon and Kirchoff, who previously had published a review of the period 1900-1930. The later article, containing 455 references, noted that various factors have been studied in the etiology of lung cancer, including tuberculosis, influenza and other chest diseases, occupational exposures, atmospheric pollutants, and tobacco. It concluded that the cause of human lung cancer is unknown.

Medical Student Fellowships

Since 1955 the Tobacco Industry Research Committee has, upon recommendation of the Scientific Advisory Board, been supporting a program designed to stimulate interest in basic research among medical school students. This program was again in effect during the year among the nation's accredited medical and osteopathic schools.

The importance of such a program was recognized in the April 1961 report of the President's Conference on Heart Disease and Cancer. This report said that basic research must be supported as the chief source of new knowledge and urged that more young people of outstanding ability be recruited into the health field.

Under the fellowship program of the T.I.R.C., students, in consultation with their advisors, select the subjects they wish to study. Deans of the schools choose the fellows, and the work is done during summer or other off-term times under the supervision of experienced researchers. In the last seven years more than 500 young persons have received fellowships offered by the Scientific Advisory Board.

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Abstracts of Reports

Each recipient of a Tobacco Industry Research Committee grant-in-aid is responsible for the initial presentation or publication of the results of his research in scientific meetings or in appropriate scientific journals.

Following are abstracts, approved by the authors, of research reports, with acknowledgement of support from the T.I.R.C., that have appeared in scientific journals since the last Report of the Scientific Director and through December 1961. The name of the scientist to whom the T.I.R.C. grant was made is given in parentheses where required. Copies of abstracts in previous Reports are available upon request.

These abstracts have been grouped under six headings: I. Cancer Research; II. Human Lung Studies; III. Cardiovascular Studies; IV. Psychophysiological Studies; V. Tobacco Chemistry and Biochemistry; and VI. Other Studies.

I. *Cancer Research*

"TUMOR-HOST RELATIONSHIPS STUDIED *IN VITRO:* EXPERIMENTS WITH CELL-FREE SYSTEMS." By Leopold R. Cerecedo, Sister Marian Jose Smith, and Jesus Vicente, Department of Biochemistry, Fordham University, New York City, and Department of Biochemistry and Nutrition, School of Medicine, University of Puerto Rico, San Juan. *Archives of Biochemistry and Biophysics*, Vol. 92, pages 484-486, March 1961. (T.I.R.C. grantee: Cerecedo)

Purpose of study: Previous studies by the authors have shown that in tumor-bearing rats there is an increase in the deoxyribonucleic acid (DNA) concentration of certain tissues at a distance from the tumor. These effects of the tumor could also be shown *in vitro* when the incorporation of thymidine-H^3 and adenine-C^{14} into the DNA in slices from tumor-bearing animals was compared with that in the tissues of control animals. It was decided to investigate whether the stimulatory effect of the tumor could also be shown in cell-free systems.

Procedure: The incorporation of thymidine-H^3 into DNA was studied in high-speed supernatants of extracts of lung, kidney, liver, and spleen of normal rats and of rats bearing the Walker 256 carcinoma and the Jensen sarcoma.

Findings: An increased incorporation was observed in the supernatants of the liver and the spleen of the tumor-bearing hosts as compared with that in the normal controls. The effect of the Jensen tumor on the incorporation was more pronounced than that of the Walker carcinoma. This increased activity was also found when the incorporation of the thymidine-H^3 was studied in the supernatant fractions of the tumors themselves. It is reasonable to assume that some factor produced by the tumor and transmitted to these tissues by way of the blood is involved in this phenomenon.

Other grantors: U. S. Public Health Service and the Damon Runyon Memorial Fund.

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"THE EFFECT OF SMOKE AND NON-SMOKE GASES ON CELLS IN CELL AND ORGAN CULTURES." By Philip Cooper, M.D., FACS, and Irene P. Goldring, Ph.D., Department of Surgery, Albert Einstein College of Medicine, and Bronx Veterans Administration Hospital, New York. *Surgical Forum,* Vol. 11, pages 72-73, 1960. (T.I.R.C. grantee: Cooper)

Purpose of study: Studies have already been accomplished on the possible effect of cigarette smoke on lung, *in vivo,* or on tissue slices, *in vitro.* The present study was initiated to investigate the effect of various gaseous agents on cells at a cellular level.

Procedures: Smoke from cigarettes, cigarette paper, or onionskin paper was injected into mammalian cell cultures. Controls included similar cultures exposed to atmospheric gases, carbon monoxide, illuminating gas, and other non-smoke gases. The gases were injected after a growth period of 24 hours into flasks containing an original inoculum of 100,000 cells in 2 cc. of NCTC-109 synthetic media to which 10 percent horse serum had been added. Three cell volumes (0.5, 1, or 1.5 cc) of smoke were injected; total cell count of each culture was made after an additional 48 hours. Daily microscopic observations were made.

Cells in a Rose perfusion chamber were observed directly after the injection of cigarette or cigarette paper smoke. Cigarette smoke was also injected into embryonic rabbit lung organ cultures. Lung organ cultures of 18 day old rabbit embryos, grown for 24 hours in synthetic media, were exposed to 5 cc. of cigarette smoke, and sections were prepared from the tissue after an additional 48 hours.

Findings: All smoke gases tested altered the growth curve of the cultures significantly, and a reduced cell population resulted. The changes induced by cigarette paper or onionskin paper smoke were more pronounced than that produced by cigarette smoke. Non-smoke gases tested showed no significant effect. Cells grown in a perfusion chamber became enlarged, showed surface "blebbing", and increased cytoplasmic granularity and vacuolation. The embryonic lung organ cultures showed arrest of growth and degenerative changes in the tissue after exposure to cigarette smoke. The effect of the smoke gases, over prolonged periods, may conceivably produce chronic inflammatory changes in the lung.

"A PROTOZOAN ASSAY FOR CARCINOGENIC HYDROCARBONS." By Robert W. Hull, Ph.D., Department of Biological Science, Northwestern University, Evanston, Ill. *Proceedings, International Conference of Protozoology,* Prague, Czechoslovakia, Aug. 24, 1961.

Purpose of study: Although the basic mechanisms of photodynamic action are still unknown, exploitation of the phenomenon of response of Protozoa to ultraviolet and related radiation for use in the detection of hydrocarbons in high dilution can have considerable utility in the area of cancer research.

Procedure: Solutions of hydrocarbons in water are prepared by either of two methods. The ciliates in an amount of glass-distilled water equal to the volume of hydrocarbon solution are added to Pyrex spot test plates or standard slides containing the suspensions. The ciliates are concentrated so as to provide between 20 and 30 ciliates per depression. The ciliates

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routinely used are *Paramecium caudatum* grown in axenic media or in media containing *Aerobacter aerogenes*. Controls in the test are ciliates handled in exactly the same manner except that the hydrocarbon is omitted. The ciliates in the hydrocarbon suspensions are held in total darkness for one hour or more and then exposed to light of known quality and intensity. The time intervals between onset of exposure and immobility of 90 percent of the ciliates is recorded. The effects of various known light wave-lengths between the maximum bacteriocidal wave-length and visible light were examined.

Findings: The work done to date deals with standardization of the assay technique as regards its 1) reproducibility and range of sensitivity, 2) the effect of the quality of the irradiating light, 3) the effect of various intervals of exposure of the ciliates to the test compounds prior to irradiation, and 4) variations in sensitivity to a series of different hydrocarbons, some of which are established carcinogens. In general, hydrocarbons that are known from mammal tests to be carcinogenic show a shorter kill-time in the assay system than do hydrocarbons whose carcinogenicity has not been established. This assay predicts that certain of these compounds tested will be found to be effective carcinogens.

It can be concluded from the data now at hand that this assay system is sensitive and reliable in the detection of polycyclic hydrocarbons in high dilution. It can be anticipated that further characterization of the test may provide accurate prediction of carcinogenic potency of the hydrocarbons. There is also the very real possibility that this assay system may provide a means for direct attack on the basic mechanisms of chemical carcinogenesis.

"QUANTITATIVE CYTOCHEMICAL STUDIES ON THE RELATION OF DEOXYRIBONUCLEIC ACID OF CELLS TO VARIOUS PATHOLOGICAL CONDITIONS." By Cecilie Leuchtenberger, Ph.D., and Rudolf Leuchtenberger, M.D., The Children's Cancer Research Foundation, Boston, Mass. *Biochemical Pharmacology*, Vol. 4, pages 128-163, August 1960. (T.I.R.C. grantee: Cecilie Leuchtenberger)

Purpose of study: The possibility of a direct correlation between the functional stage of a cell, be it normal or abnormal, its microscopic appearance and its chemical composition assumes particular significance in view of the fact that a change in function and morphology of a cell is more or less the expression of underlying and often preceding chemical alteration. Simultaneous morphological and chemical investigation at the single-cell level might not only throw light on etiology and pathogenesis but also might help greatly in the detection and understanding of disease. In particular, special attention to the study of deoxyribonucleic acid (DNA) in abnormal cells and in cells under pathologic conditions seemed merited in view of the important role of DNA for cell life and cell continuity, its quantitative stability under normal conditions, and its close relationship to the genes.

Procedures: During the last 10 years the quantitative behavior of DNA in cells has been extensively investigated by microspectrophotometry and interference microscopy in relation to four pathological processes: (1) surgical stress, (2) tumors, (3) virus infections, and (4) infertility. In studying (1), dogs were subjected to gastrectomy and cholecystectomy, and

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cells of liver and adrenals were analyzed for DNA content. In the case of (2), human precancerous and tumor tissues were studied and contrasted with normal human tissue. Under (3) different types of human and other cells infected with different DNA-containing viruses were examined *in situ* in the host and in tissue cultures, and in (4) more than 32,000 sperm cells from over 200 men and from over 100 bulls were analyzed for DNA content.

Findings: (1) Analysis of more than 7,000 individual cells from livers and adrenals from 17 dogs showed that DNA content remained unchanged after surgical stress, although a considerable elevation of tyrosine was noted in liver cells and in cells of the adrenal medulla after surgery. (2) It was found that all normal tissues, no matter what their origin or metabolic function, contained cells with a similar basic mean DNA content, whereas the DNA content of precancerous lesions and malignant tumors was found to be increased and revealed a much larger scatter from cell to cell. The deviating DNA data cannot be considered a specific criterion for malignant transformation of cells, but may be explained mainly on the basis of growth and mitotic processes present in most tumors. On the other hand, constancy of DNA in normal tissues indicates that an increase and large scatter of DNA in such tissue must be looked upon with suspicion of malignancy, unless regeneration is to be expected. Benign cells disclosed essentially a normal constant DNA quantity. (3) Study of different types of cells infected with different DNA-containing viruses *in situ* in the host and in tissue cultures revealed a peculiar combination of intranuclear bizarre conglomeration of DNA masses associated with striking increase and variability of DNA. This almost specific response of cells to an infection with a DNA-containing virus was noted irrespective of the type of such virus (verruca vulgaris, adenovirus, etc.), of the species and types of cells infected (human, insect, normal, or cancer cell), or whether the cells were still *in situ* or explanted in tissue culture. (4) In contrast to the remarkably constant and uniform haploid DNA content in sperm from fertile human males and bulls, the DNA content in the sperm from infertile males was frequently variable and significantly lower than that from fertile ones.

In addition to the various types of human tumors studied, the relation of DNA to spontaneous and transplanted animal tumors was also investigated. Principally there were no essential differences between the DNA behavior in human and in animal tumors studied. This similarity of DNA response deserves special consideration, because some of the animal tumors studied were tumors with a known viral etiology, namely Rous sarcoma of the chicken and Polyoma tumors of mice.

Other grantors: U. S. Public Health Service, Brush Foundation, Elsa E. Pardee Foundation, and Franchester Fertility Fund of Cleveland, O.

"A CORRELATED HISTOLOGICAL, CYTOLOGICAL AND CYTOCHEMICAL STUDY OF THE TRACHEOBRONCHIAL TREE AND LUNGS OF MICE EXPOSED TO CIGARETTE SMOKE." By Cecilie Leuchtenberger, Ph.D. and Rudolf Leuchtenberger, M.D., Institut für Allgemeine Botanik, ETH, Zürich, Switzerland, *Acta Medica Scandinavica*, Volume 170, Supplement 369, pages 102-118, 1961.

On the basis of the data presented so far, it appears that exposure to cigarette smoke will evoke alterations in the bronchi of some mice sum-

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marized as follows: 1. No significant histological changes. 2. Mild bronchitis; swollen epithelium frequently associated with mild hyperplasia. 3. Severe bronchitis and peribronchitis; atypical basal cell hyperplasia, squamous cell metaplasia and occasionally histopathological changes consistent with the terms "dysplasia" or "carcinoma *in situ*." One or more of the above changes may be observed in the same animal.

Although, on the evidence of these findings, one may be tempted to conclude that there is a direct cause-effect relationship between cigarette smoke and the epithelial lesions, there are mainly two findings in our study which impose caution against drawing such a conclusion:

1. A striking difference of response is encountered from mouse to mouse which occurs regardless of whether mice were exposed to relatively low doses of cigarette smoke for a brief period or a relatively high dose of cigarette smoke for a long period. In each of the groups, over 50 percent of the mice did not show any bronchial lesions, while 25 percent showed mild and 20 percent dysplastic lesions.

2. There is absence of a relationship between dose and length of exposure to cigarette smoke and frequency and severity of lesions produced. It is evident that, in spite of the considerable increase in length of exposure and number of cigarettes, the relationship between mice showing no significant changes and mice showing mild and severe changes in the bronchial tree did not alter appreciably. It is indeed astonishing that, among the last group, no invasive bronchogenic carcinoma has been observed although these mice had been exposed to enormous quantities of cigarette smoke, and, whenever possible, for nearly their whole life span.

The wide spectrum of findings and the independence of dose and duration of exposure to cigarette smoke would seem to detract from the importance of cigarette smoke as an injurious agent invariably affecting the major bronchi and would, rather, point to contributing factors characteristic for the individual animal. Among the many possible host factors, viruses deserve special consideration — the more so since they occur with a certain frequency in mice, sometimes in a latent form, and are capable of producing respiratory lesions and proliferation of bronchial epithelium.

There are two main lines which we are investigating at present. The first is concerned with the detection of latent viruses in mice prior to exposure to cigarette smoke. The second is concerned with the effect of exposure to virus in addition to the exposure to cigarette smoke.

"COMMON HUMAN VIRUSES AS CARCINOGEN VECTORS." By Christopher M. Martin, M.D.; Sigmundur Magnusson, Fellow of the Squibb Institute for Medical Research Foundation; Philip J. Goscienski and Gerald F. Hansen, National Institutes of Health research fellows; Seton Hall College of Medicine, Jersey City, N. J. *Science*, Dec. 15, 1961, pages 1985-1986. (T.I.R.C. grantee: Martin)

Purpose of study: It has been a continuing paradox that carcinogens strongly implicated in human tumorigenesis, though present in the human environment in only trace amounts, ordinarily will induce neoplasia in animals only when administered in relatively large amounts or with various physical or chemical "co-carcinogens." Speculation on possible natural

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co-carcinogens led to consideration of the possible role of common, non-tumor viruses.

Procedures: Studies were performed *in vivo* on 280 male Swiss white mice from a colony proved free of polyoma virus and which were reported to have a low incidence of *de novo* tumors. Pairs of known chemical carcinogens and common viruses in different combinations were administered by injection. The viruses used (vaccinia, ECHO 9, Coxsackie B_1 and poliovirus 2) were harvested fluids of fully infected tissue cultures of monkey kidney; by the routes given, they evoked negligible mortality or morbidity. The carcinogens injected and their respective doses, judged to be too small to induce tumors, were 100 micrograms each of 9,10-dimethylbenzanthracene-1,2 (DMBA) or of 2-aminofluorene (AF), and 75 micrograms of 1,2;5,6-dibenzanthracene (DBA).

To determine the role of immunization, half of a group of 108 additional mice were immunized against vaccinia virus and half against frozen-thawed monkey kidney cells prior to administration of either vaccinia virus or frozen-thawed monkey kidney cells plus either DMBA or propylene glycol.

Findings: Malignant tumors occurred in 5 groups of mice that received carcinogen-virus pairs, and in no other groups. There were 5 malignant tumors each among 16 mice injected with DMBA and vaccinia virus, 9 of which were living at 3 months, and among 12 mice injected with DMBA and poliovirus 2, 7 of which survived to 3 months. There were 2 tumors each among 12 mice injected with AF and ECHO 9 virus, with 7 living at 3 months, and among 12 mice injected with AF and Coxsackie B_1 virus, of which 6 survived to 3 months. Four thymomas — tumors known to arise *de novo* in this mouse strain — occurred in the 161 mice alive after 3 months.

After 8 months, the only tumors observed in the immunization experiment mice were 4 lymphomas in a group of 8 mice that were not immune to vaccinia virus and were given vaccinia and DMBA intraperitoneally.

In vitro studies: Carcinogen-binding by Poliovirus 2—approximately 10,000 molecules *per virus* tissue culture, 50% of infectious dose — was demonstrated *in vitro*, with the use of DMBA-9-C^{14}.

The results affirm *in vivo* interactions of viruses and carcinogens previously described by other investigators, and are consistent with the report by D. V. Wiseley et al. (Proc. A.A.C.R. *3*:278, 1961) of enhanced chemical carcinogenesis in mice repeatedly exposed to respiratory viruses. If such interactions occur in nature, it may prove possible to reduce neoplasia currently ascribed to chemical carcinogens by immunization against a virus.

"CHANGES IN MODAL VALUES OF CHROMOSOMES AFTER IRRADIATION OF HUMAN AMNION CELLS." By Masahiro Mizutani, B.A., and Y. H. Nakanishi, Ph.D., now at Hokkaido University, Japan; Yasushi Ohnuki, M.S., now at Pasadena, Cal., Foundation for Medical Research, and C. M. Pomerat, Ph.D., Tissue Culture Laboratory, Department of Anatomy, University of Texas Medical Branch, Galveston. *A.C.S.*

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Conference in Research on the Radiotherapy of Cancer, pages 56-69, April 1961. (T.I.R.C. grantee: Pomerat)

Purpose of study: Cytological examination of irradiated cells of whole organisms of many workers invite studies in this field, with the use of cell cultures, of successive gamma radiation on the modal chromosomal number of a human amnion strain.

Procedure: A human amnion cell strain with a modal value of 75 chromosomes was cultivated for two days prior to irradiation with 1000 r of gamma rays from a radioactive cobalt source. The observation of chromosomes was made with the use of phase contrast microscopy.

Findings: The population of human amnion cells showed severe injury from the radiation. On cultivation, healthy looking cells were restored; however, they now had 73 chromosomes. Repetition of the treatment on the new subline reduced the modal value of chromosomes to 71. Further reduction of this value did not occur after irradiation for the third and even for the fourth time. Other human amnion cells were irradiated four times during 50 days without making subcultures. The most frequent chromosome number at the eleventh sub-culture of the established subline dropped from 75 to 71. The stopping of the modal value at 71 invites further studies concerning this type of radioresistance.

"SOME COMPARATIVE EFFECTS OF SMOKED PAPER, TOBACCO AND CIGARETTES ON CHROMOSOMES *IN VITRO*." By Akio Awa, Yasushi Ohnuki, and C. M. Pomerat, Pasadena (Cal.) Foundation for Medical Research, *Texas Reports on Biology and Medicine*, Vol. 19, pages 518-528, Fall 1961. (T.I.R.C. Fellows: Awa and Ohnuki)

Mitotic and chromosomal analyses were carried out in the HL-C strain cells exposed directly to the smoke collected from (A) whole cigarettes, (B) tobacco alone, and (C) paper alone. Morphological observations revealed that paper smoke induced severe vacuolization of the cytoplasm together with pycnotic nuclei in most cells. In contrast, little evidence of cellular damage was shown by exposure of smoke from whole cigarette and from tobacco alone.

There was a decrease in the rate of the mitotic index and a considerable increase in the number of abnormal divisions as a result of the treatment with each substance, particularly with paper smoke. Contraction of chromosomes was noticed in some metaphases exposed to smoke from whole cigarettes and from tobacco. In contrast, paper smoke produced a high incidence of chromosome stickiness.

These mitotic abnormalities and the shift in the modal chromosome number of the HL-C strain are briefly discussed.

Other grantor: U.S. Public Health Service.

"PULMONARY NEOPLASMS PRODUCED BY METHYLCHOLANTHRENE IN THE WHITE PEKIN DUCK." By R. H. Rigdon, Department of Pathology, University of Texas Medical Branch, Galveston. *Cancer Research*, Vol. 21, pages 571-574, May 1961.

Purpose of study: The respiratory tract in the duck is similar in many ways to that in man. In previous experiments carcinomas and sarcomas occurred in the respiratory tract of white Pekin ducks given an intra-

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tracheal injection of methylcholanthrene suspended in polysorbate 80. More detailed investigation was considered desirable.

Procedure: Sixty-six ducks were given 3-methylcholanthrene suspended in a 1 percent aqueous solution of polysorbate 80, and 25 were given only the polysorbate. A small catheter was placed in the trachea through the external larynx, and one 25 ml. injection of the solution was given within an interval of 2 to 3 minutes; 250 mg. of methylcholanthrene was given to 22 ducks, 125 mg. to 28, and 62.5 mg. to 16. The birds were sacrificed or died at varying intervals, and the respiratory tract removed *in toto* for examination.

Findings: No tumors occurred in birds receiving polysorbate alone, but striated amyloid in the liver, and local areas of necrosis in striated muscle, appeared in some of these ducks. Many neoplasms occurred in the respiratory tract of birds receiving methylcholanthrene, the first appearing 56 days after injection. Some of the tumors were neurofibromas, and others were ganglioneuromas, hemangiomas, squamous cell-like carcinomas, adenocarcinomas, and unclassified types of tumors. Frequently a single tumor showed a variety of histological patterns. No metastases occurred. Methylcholanthrene crystals persisted in the tract for long periods. Since amyloid and muscular necrosis appeared in treated ducks and the controls, these effects do not appear specifically related to methylcholanthrene. The problem of amyloidosis in the duck is now under study.

Other grantor: U. S. Public Health Service.

"LESIONS IN DUCKS GIVEN METHYLCHOLANTHRENE." By R. H. Rigdon, M.D., and S. M. McAnelly, B.A., University of Texas Medical Branch, Galveston. *Archives of Pathology*, Vol. 72, pages 455-464, October 1961. (T.I.R.C. grantee: Rigdon)

Purpose of study: In a previous experiment neoplasms developed in the respiratory tract of white Pekin ducks following a single intratracheal injection of methylcholanthrene. The present study was made to observe the pathologic changes occurring in the respiratory tract preceding the development of neoplasms.

Procedure: Twenty milliliters of a solution of 50 mg. of methylcholanthrene in polysorbate was injected by tube into the trachea of 20 ducks 56 days old; 2 of these birds were killed 5½ hours later, 2 after 7 days, 2 after 13 days, and 3 died on the 26th and 27th day. One was killed on the 35th day and 10 were killed on the 84th day following the injection. Ten other birds 40 days old were given 6 to 9 daily injections and 10 others were given 10 mg. for 7 to 16 times; all ducks given multiple injections either died or were killed at intervals of 9 to 72 days following the first injection of the carcinogen. The respiratory tract including only the lower third of the trachea was removed and several sections taken for histologic study.

Findings: An acute and chronic inflammatory reaction occurs in the lung of white Pekin ducks following the intratracheal injection of methylcholanthrene in polysorbate 80. Associated with this inflammatory reaction is regeneration, hyperplasia, and metaplasia of the bronchial epithelium. Metaplasia occurs as early as 7 days after treatment. Hemangiomas, adenocarcinomas, and fibrosarcomas are present in the lungs 72 days following the

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first of 16 intratracheal injections of the carcinogen. In view of the presence of squamous metaplasia and the absence of typical squamous-cell carcinomas in the lungs of these ducks the question is raised referable to the pathogenesis of these neoplasms. Methylcholanthrene crystals mechanically obstruct the lumen of the small bronchi resulting in atelectasis and subsequently pulmonary fibrosis with an associated pulmonary emphysema.

Other grantor: U. S. Public Health Service.

II. *Human Lung Studies*

"ACUTE EFFECTS OF INHALATION OF CIGARETTE SMOKE ON AIRWAY CONDUCTANCE." By Jay A. Nadel and Julius H. Comroe Jr., Cardiovascular Research Institute, University of California Medical Center, San Francisco. *Journal of Applied Physiology,* Vol. 16, pages 713-716, July 1961. (T.I.R.C. grantee: Comroe)

Purpose of study: Previous studies of the acute effects of inhalation of cigarette smoke on "airway resistance" are of doubtful significance, a) because some of the methods used require an initial deep inspiration, which we now know may itself decrease airways resistance, and b) because none of the tests measured airway resistance alone but rather a combination of factors, including tissue resistance and voluntary muscular effort. Accordingly, we used the body plethysmograph technique to obtain a sensitive measurement of airway resistance alone.

Procedure: Each subject sat in the closed 900-liter body plethysmograph for a few minutes, then panted through a flowmeter for several seconds, during which time his airway resistance was measured at flow rates of 0.5 liter per second. We then closed a shutter between the mouthpiece and the flowmeter and measured the subject's thoracic gas volume (TGV) plethysmographically. Each test consisted of four consecutive measurements of airway resistance and TGV. We calculated all data as airway conductance (1/resistance)/TGV to correct for variations in lung volume during testing. We tested 48 subjects whose lungs were normal, including male and female smokers and non-smokers, and 22 patients with a diagnosis of pulmonary emphysema, asthma, pulmonary fibrosis, sarcoidosis, or mitral stenosis, all cigarette smokers.

Findings: In the healthy subjects there was no significant difference between male and female smokers and male non-smokers, but airway conductance/TGV was significantly higher in female non-smokers in the control state. We studied the acute effect of cigarette smoke inhalation in 36 healthy subjects (21 smokers and 15 non-smokers) and 22 smokers with cardiopulmonary disease; the airway conductance/TGV ratio decreased after the inhalation of cigarette smoke in both groups. The effects were almost immediate; the mean duration of effect was 35 minutes. Inhalation of 0.5 percent isoproterenol aerosol reversed or prevented the effect of cigarette smoke inhalation. The decrease in conductance/TGV caused by inhalation of cigarette smoke did not appear to be related to inhalation of nicotine or of other volatile substances.

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Our study indicates that mild bronchoconstriction, insufficient to cause symptoms, occurs immediately in most individuals after inhalation of cigarette smoke, lasts 10-80 minutes, and reoccurs with a second cigarette. We suggest that there are insufficient and inadequate data at present to warrant relating the "bronchoconstriction" of smoking causally to the initiation or aggravation of chronic pulmonary disease.

Other grantor: U. S. Public Health Service.

"THE PATHOLOGIC ANATOMY OF THE BRONCHIAL TREE AND LUNGS." By Stanley P. Reimann, M.D., Director Emeritus, Institute for Cancer Research, Philadelphia, Pa., and Member, Scientific Advisory Board to the Tobacco Industry Research Committee. *Archives of Pathology,* Vol. 70, pages 757-762, December 1960. (T.I.R.C. grantee: Pathologic — Anatomic Study Group)

Twelve experienced pathologists from various parts of the United States undertook a study of the pathologic anatomy of the bronchial tree and lungs in specimens obtained from routine autopsy services and surgical excisions. The object was to catalogue changes, sites and incidence in these organs in relation to age, sex, occupation, place of residence and work, use of tobacco, and cause of death. The classifications used were: normal, hyperplasia, squamous metaplasia, atypical metaplasia, carcinoma *in situ,* carcinoma.

About 3,000 cases were investigated yielding 8,590 slides from males and 3,661 slides from females adjudged suitable. The border line cases provoked disagreements, many of which could not be reconciled. In addition to conferences, selected slides were circulated and many pathologists re-examined their own slides a year or so after their original diagnosis. Some of the limitations of the practice of pathologic anatomy were discussed.

From raw compilations the results were equivocal. Rigid statistical appraisals were made and were published in separate papers (E. B. Wilson & M. H. Burke, 1957-60). It was shown that a cooperative study is needed in problems in which large amounts of data must be collected and in which basic procedures in a particular discipline can be collectively assessed.

"A STUDY OF THE TRACHEOBRONCHIAL EPITHELIUM AND CHANGES RELATED TO SMOKING." By K. R. Cross, M.D., Donald V. Walz, M.D., G. Keith Palmer, M.D., and E. D. Warner, M.D., Department of Pathology, Veterans Administration Hospital, Iowa City, Ia. *Journal of the Iowa State Medical Society,* Vol. 51, pages 137-140, March 1961. (T.I.R.C. grantee: Warner)

Purpose of study: Of the first 915 autopsies at the Hospital during a six-year period bronchogenic carcinoma was diagnosed in 139 cases (15 percent). The purpose of this paper is to discover the degree and type of metaplastic changes occurring in the bronchial epithelium and to determine whether or not these changes are related (1) to previous smoking, and (2) to the development of bronchogenic carcinoma.

Procedure: Fifteen representative sections of the trachea and the large and small bronchi were selected in each of 140 autopsy cases proved suitable for study, including 26 patients with carcinoma of the lung. The sections were classified as normal, hyperplasia, squamous metaplasia, atypical metaplasia, carcinoma *in situ,* and carcinoma. There were 31 non-smokers,

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19 light, 13 moderate, 56 heavy, and 21 very heavy smokers among the 140 cases.

Findings: The bronchial tissues of only 48 percent of the cases could be considered normal, comprising 44 percent of the sections from smokers and 61 percent of the sections from non-smokers. Carcinoma was found only among smokers, as was carcinoma *in situ,* and the latter was found only in patients with lung cancer; the 7 instances found were fewer than one would expect if carcinoma *in situ* had preceded the development of carcinoma of the lung. Although the study fails to support the premise that carcinoma arises from pre-existing atypical metaplastic changes in bronchial epithelium, it is evident that there is a significant association between certain epithelial changes in the tracheobronchial tree and the presence of malignancy. It would seem that a history of cigarette smoking is significantly related to the incidence of carcinoma, and therefore difficult to ignore. A final determination of the relationship between smoking and these pathological changes will require much more study.

III. *Cardiovascular Studies*

"EFFECT OF CIGARETTE SMOKING AND NICOTINE ON SERUM FREE FATTY ACIDS." By Alfred Kershbaum, M.D., Samuel Bellet, M.D., Edward R. Dickstein, M.D., and Leonard J. Feinberg, Ph.D., Division of Cardiology, Philadelphia General Hospital. *Circulation Research,* Vol. 9, pages 631-638, May 1961. (T.I.R.C. grantee: Bellet)

Purpose of study: It seemed important to investigate how the effects of nicotine influence the metabolism of lipids, particularly since recent studies have shown that free fatty acids (FFA) are rapidly released into the circulation from tissue fat deposits following the administration of epinephrine and norepinephrine and following stress effects on the sympathetic nervous system.

Procedures: Patients and personnel at Philadelphia General Hospital were selected at random, including 7 normals, 7 coronary heart disease cases, and 17 patients with various other diagnoses, aged 16 to 72, including non-smokers as well as smokers. All tests were made at 9 a.m. in fasting condition. In 17 subjects, 2 cigarettes were smoked within a 10-minute period. Blood samples were taken before smoking, immediately thereafter, and at 10, 20 and 40 minutes after cessation of smoking. Another group of 9 subjects served as controls to determine what effect the experimental procedure itself would have (fasting, preparation, venipuncture, etc.). Several of the controls inhaled deeply to simulate smoking during the initial 10-minute period. Each of 5 subjects smoked 6 cigarettes in 40 minutes to study the effect of "chain smoking" and FFA concentrations were determined at 10-minute intervals for a total period of 60 minutes after smoking ended.

Findings: In all 17 subjects who smoked 2 cigarettes the FFA levels rose at the end of the smoking period, maximum elevation occurring 10 minutes later. Twenty and 40 minutes after smoking the FFA levels were still above the presmoking level in most instances. The FFA response did not appear to be related to age, sex, smoking habits, type of cigarette used, or pre-

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smoking level of FFA. There was essentially no change in the serum total cholesterol or triglycerides during the experimental period. There was a slight increase in FFA over a 20-to-40 minute period in the nonsmoking controls, slightly above that anticipated from fasting alone. The five subjects who "chain-smoked" all developed FFA elevations which persisted during the 60 minutes of observation.

An eventual, delayed increase in serum levels of cholesterol and other lipoprotein lipids, as occurs in animals after epinephrine, is a conceivable result in humans after smoking. This, at least, suggests an explanation for the higher cholesterol levels often found in smokers. If, as many investigators believe, a disturbance of lipid metabolism is a factor in the development of atherosclerosis, the effect of cigarette smoking on lipid metabolism should be given attention in considering the pathogenesis of this disorder.

Other grantor: U. S. Public Health Service.

"THE RELATIONSHIP BETWEEN BIOCHEMICAL ACTIVITY AND MECHANICAL FUNCTION OF THE HEART." By R. J. Bing, M.D. *Proceedings, 6th International Congress of Internal Medicine,* Basel, Switzerland, 1960.

Recent studies have further defined the myocardial utilization of fatty acids, and reveal that, in the fasting human, the mean myocardial extraction of free fatty acids accounts for 42 percent of the total fatty acid extraction, while the esterified fraction makes up the other 58 percent. Since oleic acid appears to be the fatty acid primarily used by the heart, it appears that, in contrast to previous conclusions, the myocardium uses preferentially unsaturated fatty acids.

In the most common types of heart failure, absence of alterations in utilization of oxygen and substrate by the heart probably denotes absence of involvement of metabolic factors within the heart. This by exclusion points to the organs of energy utilization, the contractile proteins, as the site of the derangement in the myocardium in this group. Studies undertaken on actomyosin bands, although not yet conclusive, support this contention. Thus, it has been shown that the contractility of these bands from hearts of human subjects dying from congestive failure is impaired.

While there is no doubt that the blood concentration of catecholamines influences myocardial function, the pharmacologic role of catecholamines stored in the heart muscle remains unsolved. The release of stored catecholamines is of interest because it is relevant to the main topic of this discussion, the relation of functional activity of the heart to the integrated enzyme activity. The pharmacologic importance of the stored catecholamines is as yet uncertain.

This review suggests that work on cardiac metabolism has moved from the search for utilization of substrates by the heart to the investigation of the relationship between biochemical and mechanical function.

"MYOCARDIAL RESPONSE TO CIGARETTE SMOKING IN NORMAL SUBJECTS AND PATIENTS WITH CORONARY DISEASE." By T. J. Regan, M.D., M. J. Frank, M.D., J. F. McGinty, M.D., E. Zobl, M.D., H. K. Hellems, M.D. and R. J. Bing, M.D., Department of Medicine, Wayne State University College of Medicine, Detroit, Mich. *Circulation,* Volume 23, pages 365-369, March 1961. (T.I.R.C. grantee: Bing)

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Purpose of study: In a previous study the early response to cigarette smoking was associated with enhanced myocardial blood flow in normal subjects. Whether a similar situation occurs after the known peripheral hemodynamic responses have been established and maintained required examination. To assess the potential role of tobacco as a cause of myocardial ischemia, the response to smoking in patients with coronary artery disease has been contrasted with that occurring in control subjects.

Procedures: The study group comprised 8 subjects with coronary artery disease who had incurred an acute myocardial infarction at least one year previously and 6 control subjects who had recovered from acute benign illnesses. All the patients were habitual smokers. After an overnight fast, the patient was catheterized through the coronary sinus and right atrium and a needle was placed in the brachial artery. Resting coronary blood flow was determined in the recumbent position and the patient began cigarette inhalation at 45-second intervals. Two standard non-filter cigarettes were consumed in about 25 minutes, so that the initial increase of pulse rate and pressure was largely maintained during the subsequent 12 minutes of nitrous oxide inhalation. Upon cessation of inhalation, cigarette smoking was resumed at the same rate and was maintained throughout the coronary blood flow sampling. Heart rate, arterial pressure, and a left ventricular lead were monitored throughout the smoking and were relatively constant during this procedure.

Findings: During cigarette smoking both the coronary and control groups had significant acceleration of heart rate. A uniform rise of arterial pressure was seen in the latter and, with one exception, in the coronary group. Further, there was a tendency for these hemodynamic changes to be more pronounced in the coronary group. All control subjects had an increase in cardiac index as did all but two in the coronary group. A uniform increment of left ventricular work during smoking was also more pronounced in the coronary group.

The attendant changes in coronary blood flow were not significant in either group. This phenomenon, combined with an unaltered myocardial oxygen extraction, resulted in a virtually identical myocardial oxygen usage as in the control state. There was no evidence of myocardial ischemia in the coronary subjects during smoking. Failure to find increases of myocardial blood flow and oxygen usage in the coronary subjects during cigarette smoking may plausibly be related to the "fixed coronary resistance" alleged to exist in such patients. That the abnormal coronary vasculature is not responsible becomes apparent from the similar response in the subjects without evidence of coronary disease.

Other grantors: U. S. Public Health Service, American Heart Association, Michigan Heart Association, Life Insurance Medical Research Fund, Abbott Laboratories, and the Burroughs-Wellcome Fund.

"STORAGE OF CATECHOLAMINES IN THE HEART. EFFECT OF AMINE OXIDASE INHIBITORS." By Kyohei Kako, M.D., Athanasios Chrysohou, M.D., and Richard J. Bing, M.D. *American Journal of Cardiology*, Volume 6, pages 1109-1111, December 1960.

"FACTORS AFFECTING MYOCARDIAL STORAGE AND RELEASE OF CATECHOLAMINES." By Kyohei Kako, M.D., Athanasios Chrys-

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ohou, M.D., and Richard J. Bing, M.D. *Circulation Research,* Volume 9, pages 295-299, March 1961.

The factors affecting myocardial storage and release of catecholamines were investigated in these two studies. The addition of dihydroxyphenylalanine (Dopa) to the perfusion fluid of a heart-lung preparation markedly increased the cathecholamine concentration of the isolated heart. *In vivo,* the combination of iproniazid and Dopa had the same effect, while iproniazid alone failed to influence myocardial amine concentration.

In animals pretreated with Dopa and iproniazid, nicotine caused a significant decrease in myocardial catecholamines. It is likely that stimulation of the adrenal medulla and sympathetic nerve endings by nicotine elevated catecholamine levels in blood, with subsequent storage in the heart and other organs.

"METABOLIC ACTIVITY OF THE INTACT HEART." By Richard J. Bing, M.D. *American Journal of Medicine,* Volume 30, pages 679-691, May 1961.

The difference in composition of blood collected from an artery and from the coronary sinus is determined by the processes of intermediary metabolism in the heart muscle cell; but because of storage of substrates and their interchange in heart muscle, the coronary arteriovenous difference reflects only a balance and permits no conclusions as to the pathways of intermediary metabolism in the heart muscle cell.

The limitations of such biochemical observations are exemplified by studies on the nitrogen equilibrium of the body. This furnishes information on the balance between dietary protein and its relation to protein breakdown or protein synthesis; but such studies tell nothing of the rate and degree of deamination, transamination, decarboxylation, or other intermediary processes of protein metabolism. It is therefore essential to combine metabolism balance studies with investigations of cellular metabolism. This report is primarily concerned with *in vivo* studies of metabolism of the normal heart, the anoxic heart, and the diabetic heart.

"EFFECT OF ATRIAL AND VENTRICULAR FIBRILLATION AND VENTRICULAR TACHYCARDIA ON CARBOHYDATE METABOLISM OF THE HEART." By Michael Klarwein, Ph.D., Kyohei Kako, M.D., Athanasios Chrysohou, M.D., and Richard J. Bing, M.D. *Circulation Research,* Volume 9, pages 819-825, July 1961.

Changes in the ratio phosphorylase-a/total phosphorylase in heart muscle, as well as the myocardial concentrations of glycogen, glucose-6-phosphate (G-6-P), lactate, pyruvate, fructose-1, 6-diphosphate (FDP), dihydroxyacetone phosphate (DHAP), were followed during artificially induced ventricular tachycardia, ventricular fibrillation, and atrial fibrillation. These experiments were carried out with and without support of the coronary circulation.

When coronary circulation was not maintained, active phosphorylase increased, then diminished in heart muscle during all three conditions, similar to changes reported in skeletal muscle. When coronary circulation was maintained, no changes in carbohydrate intermediates or in phosphorlyase-a activity were recorded. These results demonstrate that the

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metabolic changes encountered in heart muscle during these arrhythmias are the result of anoxia.

"RECENT PROGRESS AND PRESENT PROBLEMS IN THE FIELD OF SHOCK." Panel Discussion by Richard J. Bing. *Federation Proceedings,* Vol. 20, pages 72-73, July 1961.

The changes in myocardial metabolism during hemorrhagic shock are not isolated occurrences but follow the general pattern of myocardial anoxia resulting from diminished coronary blood flow. On the basis of experiments performed on the anoxic heart during ventricular tachycardia and fibrillation, it is possible that changes in phosphorylase-a activity also occur in the heart muscle during shock. Whether the enzyme phosphofructokinase is the rate-limiting enzyme in heart muscle during hemorrhagic shock remains to be established.

"CONTRACTILE PROTEINS OF HEART MUSCLE IN MAN." By Richard J. Bing, M.D. and K. Kako, M.D. *Circulation,* Volume 24, pages 483-490, August 1961, Part II.

The contractility of actomyosin bands prepared from heart muscle of patients who had died in congestive failure was diminished as compared to those prepared from normal hearts. This may have been the result of defective protein synthesis. The increase in heart rate was correlated with the activity of phosphorylase-a in heart muscle and with changes in carbohydrate intermediates (lactate, G-6-P and glycogen).

Heart rates over 300 per minute were associated with a transient increase, followed by a decrease, in phosphorylase-a activity; glycogen diminished, while lactate and G-6-P increased. The oxidation-reduction potential in heart muscle became more negative. In the absence of myocardial anoxia, the increased rate of stimulation of the heart produced no alterations in either the concentration of carbohydrate intermediates or the phosphorylase-a activity.

Alterations in function of the heart that come into play upon rapid changes of cardiac activity are the result of the integration of several diverse biochemical cellular reactions. The contractile proteins are but following the lead of the cellular elements concerned with the production of energy.

"EXTRACTION AND RELEASE OF INDIVIDUAL FREE FATTY ACIDS BY THE HEART AND FAT DEPOTS." By Martin E. Rothlin and Richard J. Bing, Department of Medicine, Wayne State University College of Medicine. *Journal of Clinical Investigation,* Vol. 40, pages 1380-1386, August 1961.

Purpose of study: It has previously been demonstrated that in the post-absorptive state energy production of the heart depends largely on fatty acid metabolism. Although the general turnover rate of individual FFA has been studied, no investigations have been undertaken to discover their fate in the heart muscle. The present study deals with the myocardial extraction of individual FFA, including its release by adipose tissue.

Procedures: Human patients free of metabolic disorders, none of whom was in congestive heart failure, and anesthetized dogs, were studied in a fasting state. Coronary venous blood of man and dog was obtained by

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catheterization of the coronary sinus; simultaneously, arterial blood was collected from the brachial artery (man) or from the femoral artery (dog). Blood from the saphenous vein (dog), which drains largely subcutaneous tissue, was also collected. Free fatty acids were determined in the various blood specimens.

Findings: In the postabsorptive state, the human as well as the dog heart extracted a consistently higher percentage of free oleic acid than of any other FFA present in arterial blood. This acid was also released at a higher rate of fat depots of the dog. These findings suggest a high turnover rate of free oleic acid. It appears likely that an exchange between plasma triglycerides and free fatty acids in heart muscle, resulting from lipoprotein lipase activity, may be responsible.

Other grantors: U. S. Public Health Service, American Heart Association, Michigan Heart Association, Life Insurance Medical Research Fund, Abbott Laboratories, and the Burroughs-Wellcome Fund.

"REHABILITATION IN HEART DISEASE." By Richard J. Bing, M.D., Detroit, Mich. *Archives of Environmental Health,* Vol. 3, pages 62-65, September 1961.

Rehabilitation in congestive failure and coronary heart disease is discussed. Proper diet and moderate exercise are important and return to work is helpful to the patient.

"CONGESTIVE HEART FAILURE. ITS PHYSIOPATHOLOGY AND TREATMENT, WITH SPECIAL REFERENCE TO INTRACTABLE HEART FAILURE." By William H. Morse and Richard J. Bing, Wayne State University College of Medicine. *Postgraduate Medicine,* Vol. 30, pages 293-300, October 1961.

The relationship between the physiopathologic factors involved in heart failure and the manifestations of the disease is not clearly understood. Clinical signs and symptoms are caused by disturbances in electrolyte and water balance.

Speculative theories have been advanced concerning the role in heart failure played by cardiac metabolic disturbances, changes in the molecular structure of actomyosin, excretion of aldosterone, release of antidiuretic hormone, and perversion of the normal mechanisms of both fluid volume and sodium regulation.

Treatment of congestive failure is still chiefly empiric, consisting of careful regulation of sodium and water intake and administration of digitalis and diuretics.

"DOPA UPTAKE AND CATECHOLAMINE CONTENT IN HEART AND SPLEEN." By A. Wegmann, K. Kako, and A. Chrysohou, Department of Medicine, Wayne State University College of Medicine, Detroit, Mich. *American Journal of Physiology,* Vol 201, pages 673-676, October 1961. (T.I.R.C. grantee: Bing)

DL-Dihydroxyphenylalanine (Dopa) was infused in mongrel dogs under various conditions in order to study its uptake and influence on the storage of norepinephrine and epinephrine in the heart and spleen. No increase in content of these catecholamines in the heart and spleen could be

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detected after Dopa infusion. Apparently the rate of conversion of Dopa into norepinephrine does not depend on the supply of the substrate.

"MYOCARDIAL METABOLISM IN PROGRESSIVE MUSCULAR DYSTROPHY." By J. F. Sundermeyer, S. Gudbjarnason, V. E. Wendt, P. B. Den Bakker, and R. J. Bing, Wayne State University College of Medicine and Harper Hospital, Detroit, Mich. *Circulation,* Vol. 24, pages 1348-1355, Dec. 1961.

The cardiac outputs were elevated in all of eleven patients with progressive muscular dystrophy studied by the authors. Differences in oxidation-reduction potential between arterial and coronary venous blood were positive, suggesting glycolysis in the heart muscle. Stimulation of glycolysis by inorganic phosphate was suggested by the relationship between inorganic phosphate concentration in blood and the myocardial glucose extraction. This suggests the possibility of uncoupling of oxidative phosphorylation in the myocardium.

"COMMON CIRCULATORY MEASUREMENTS IN SMOKERS AND NON-SMOKERS." By Henry Blackburn, M.D., Josef Brozek, Ph.D., and Henry L. Taylor, Ph.D., Laboratory of Physiological Hygiene, University of Minnesota, and Medical Department, Mutual Service Insurance Companies, St. Paul, Minn. *Circulation,* Vol. 22, pages 1112-1124, December 1960. (T.I.R.C. grantee: Brozek)

Purpose of study: No convincing theoretical or experimental basis has been established thus far to explain the higher cardiovascular mortality rates in smokers than in non-smokers shown in several epidemiological studies. The present paper is concerned with resting pulse rate and blood pressure and circulatory reactions to several pressor stimuli in male smokers and non-smokers.

Procedure: Four study groups comprising 1,093 men aged 17 to 67 were examined: group A, 286 middle-aged business and professional men; group B, 159 male university students; group C, 414 railroad employees; and group D, 234 city firemen. Replies to standardized questionnaires regarding smoking were grouped under never smoked, occasional smokers, light smokers (under 10 cigarettes daily), moderate smokers (11 to 20), heavy smokers (21 or more cigarettes daily), and stopped smoking for at least one year.

Findings: Relative body weight was consistently lower in the heavy cigarette smokers compared to those who never smoked. Basal oxygen consumption was slightly higher in smokers than in non-smokers. Pulse rate during work and recovery was significantly higher in one group of middle-aged men if pathologic cases in the group are considered. In "normal" populations, somewhat preselected for absence of hypertension, no differences in resting blood pressures were found between smokers and non-smokers. In the broader studies, involving samples of the working population, smoking was associated with lower systolic and diastolic pressures. Young student groups, with short duration of smoking habit, showed no significant differences between smokers and non-smokers.

The associations found do not provide evidence for large or important differences in circulatory reactivity between groups of habitual smokers and non-smokers. There is little evidence for deterioration of cardiovascular

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"fitness" in smokers performing work tests. The small magnitude of the differences found in circulatory measurements, plus certain sources of bias, preclude serious consideration of these factors as underlying causes of the increased mortality rate among smokers. Other unanswered questions are the importance of individual responses and hypersensitivity to smoking, and the significance of acute pressor and other effects of smoking on persons with latent or manifest cardiovascular disease.

"EFFECTS OF HYPERTENSIN ON ARTERIAL PRESSURE, HEART WORK AND CARDIAC OXYGEN UTILIZATION." By Ivan E. Forte, M.D., Louis Potgieter, Ch.B., and Jerry B. Schmitthenner, M.D., with the assistance of J. H. Hafkenschiel, M.D., and others, Division of Research, Lankenau Hospital, Philadelphia. *Circulation Research*, Vol. 8, pages 1235-1241, November 1960. (T.I.R.C. grantee: Hafkenschiel)

Purpose of study: The effects of acute increases in left ventricular pressure work on coronary blood flow, myocardial oxygen, and carbohydrate utilization required investigation. In particular, there was need for testing an experimental plan in which many observations could be made on a few animals, each serving as its own control.

Procedure: The drug Hypertensin was used, since it appears to correspond completely with the naturally occurring angiotensin, and is an agent which might increase left ventricular pressure independently of any increase in left ventricular stroke work or heart rate. Young healthy dogs were used as subjects in paired periods of observation, comparing the changes from the first to the second control period and comparing the differences found with changes observed from the control to the drug-infusion experiment. The various cardiodynamic and metabolic functions were calculated and tested for statistical significance.

Findings: The significant hemodynamic changes induced by the drug were increased mean arterial pressure and increased left ventricular work. A greater cardiac lactate utilization during the Hypertensin infusion was the only change in cardiac metabolism. The oxygen tension in left ventricular venous blood was not reduced during the action of the drug. The findings appear to support the thesis that coronary resistance is regulated to insure adequate coronary blood oxygen and lactate transport for the requirements of cardiac oxygen and lactate metabolism.

Other grantors: U. S. Public Health Service, Committee on Problems of Alcohol of the National Academy of Sciences-National Research Council, Ciba Pharmaceutical Products, Inc., and Heart Association of Southeastern Pennsylvania.

"PRACTICAL LIMITATIONS OF THE KETY METHOD FOR DETERMINING CORONARY BLOOD FLOW BY INFRARED ANALYSIS OF BLOOD NITROUS OXIDE." By Ivan E. Forte, M.S., Louis Potgieter, Ch.B., Jerry E. Schmitthenner, M.D., Hunter Neal, M.D., and J. H. Hafkenschiel, M.D., Division of Research, Lankenau Hospital, Philadelphia. *American Heart Journal*, Vol. 61, pages 81-87, January 1961.

Purpose of study: The greatest need in the area of diagnostic studies in patients with coronary artery disease is the development of a precise test to measure coronary arterial blood flow in humans, a lack of which seems

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to have been an important limiting factor in the selection of patients for, and, hence, the survival rate of those undergoing endarterectomy.

Procedure: Preliminary to attempting development of a simpler method of measuring coronary blood flow applicable to both intact animals and man, it was first necessary to learn the limitations of the Kety-Van Slyke nitrous oxide manometric as well as the direct infrared analysis techniques. The objective was to establish the reproductibility of an experimental design in which the same animals were used repeatedly, using the combined anesthesia, morphine Dial-urethane pentobarbital.

Findings: (1) The blood analytical technique using the principle of infrared absorption is practical, time saving, and comparable in precision to the manometric method. (2) During steady states the Kety nitrous oxide test is quantitative and reproducible, and, at the present time, is the best method of measuring coronary blood flow in intact animals.

Other grantors: U. S. Public Health Service, Committee on Problems of Alcohol of the National Academy of Sciences-National Research Council, Ciba Pharmaceutical Products, Inc., and Heart Association of Southeastern Pennsylvania.

"MEASUREMENT OF CORONARY BLOOD FLOW USING RADIOACTIVE IODINE COMPARED WITH NITROUS OXIDE." By Ivan E. Forte, A.B., M.S., Jerry E. Schmitthenner, M.D., and Hunter S. Neal, M.D., with the assistance of Joseph H. Hafkenschiel, M.D., and others. *Circulation Research,* Vol. 9, pages 547-551, May 1961.

Purpose of study: The theory on which this study is based is that after injection into either the pulmonary artery or left ventricle, the first activated blood to reach the right ventricle on recirculation returns by way of the coronary vessels. The answers sought are, (a) is it possible, by injecting a radioactive bolus, to record an isotope-dilution curve in the blood of the coronary sinus draining the left ventricle, and, if so, is this dilution reflected in the proximal pulmonary arterial circulation curve or in a precordial curve, and (b) if such curves are meaningful, how does myocardial blood flow and its ratio to cardiac output compare with blood-flow values recorded almost simultaneously by the nitrous-oxide desaturation method? The present report deals with question (a) alone.

Procedure: Coronary blood flow was determined by scintillation counter in anesthetized dogs before and after injections of radioactive iodine. The first two experiments attempted to obtain isotope-dilution curves while continuously injecting a radioactive sodium iodide solution, which proved unsatisfactory, and the next four experiments involved rapid injection of boluses through a catheter in the distal pulmonary artery. In the next eleven experiments, the resulting curves were compared with those obtained by the use of a catheter in the aortic root or left ventricle as the site of injection.

Findings: An isotope-dilution pattern was obtainable in only three of eight dogs tested. These results are interpreted as indicating that the radioisotope-dilution method for the determination of coronary blood flow is impracticable in the dog with present instrumentation because of the inherent uncertainty and the technical difficulties involved in the methods adopted.

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Other grantors: U. S. Public Health Service, Committee on Problems of Alcohol of the National Academy of Sciences-National Research Council, Ciba Pharmaceutical Products, Inc., and Heart Association of Southeastern Pennsylvania.

"THE ROLE OF EXERCISE TESTS IN THE DIAGNOSIS OF CORONARY ARTERY INSUFFICIENCY." By I. Forte, M.S., J. H. Hafkenschiel, M.D., J. E. Schmitthenner, M.D., H. Neal, M.D., and E. A. Daugherty, M.D., Cardiac Clinic and Research Division, Lankenau Hospital, Philadelphia. *American Heart Journal,* Vol. 61, pages 756-762, June 1961.

Purpose of study: Because of the lack of information on cardiopulmonary parameters in the early recovery period after myocardial infarction, the treadmill test was applied to a few patients in order to ascertain whether such testing is feasible as a general procedure to determine the rate of recovery and what ambulation therapy should be prescribed.

Procedure: Eight healthy volunteer male subjects aged 33 to 60 were first tested at a work load of 370 kilogram-meters per minute for 10 minutes on a treadmill (10 percent grade at 1.73 miles per hour for 10 minutes). After a 20-minute rest period, the subjects underwent another 10-minute test precisely like the first. Various cardiopulmonary parameters were recorded. Similar tests were then carried on at varying work loads with 3 postmyocardial patients and 3 patients with primary hypertension taking depressor drugs and were compared with the results with healthy subjects.

Findings: Preliminary studies on 8 healthy subjects show that the response of ventilation, oxygen uptake, and heart rate to treadmill exercise varying between 300 and 600 Kg.M./min. is linear and reproducible. Patients recovering from an acute myocardial infarction were observed to be able to tolerate an exercise work load of 370 Kg.M./min. up to 10 minutes, if able to be ambulatory. Testing at these work levels in selected patients shows that the treadmill walk can be performed without undue apprehension, excessive increases in heart rate, or marked S-T-segment displacement in the period 6 weeks to 6 months after myocardial infarction.

Other grantors: U. S. Public Health Service, Committee on Problems of Alcohol of the National Academy of Sciences-National Research Council, Ciba Pharmaceutical Products, Inc., and Heart Association of Southeastern Pennsylvania.

"CIGARETTE SMOKING AND ISCHEMIC HEART DISEASE." By B. Bronte-Stewart, M.D., MRCP, Department of Medicine, University of Capetown, and Groote Schuur Hospital, Capetown, South Africa, formerly at University of Minnesota. *British Medical Journal,* pages 379-384, Feb. 11, 1961. (T.I.R.C. grantee: Dr. Ancel Keys of the University of Minnesota). (To be read with companion pieces in same Journal: "TASTE PERCEPTION IN SMOKERS AND NON-SMOKERS." By L. H. Krut, M.B., Ch.B., Monica J. Perrin, B.Sc., Dip. Diet., and B. Bronte-Stewart, M.D., MRCP, pages 384-387, and "SMOKING AND FOOD PREFERENCES." By Perrin, Krut and Bronte-Stewart, pages 387-388.)

Purpose of study: Several epidemiological studies have reported a statistical relationship between the prevalence of ischemic heart disease and

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cigarette smoking. On examining the association one is immediately confronted with two major possibilities. Firstly, has the smoking of a cigarette a direct effect by interfering with either coronary blood flow or heart action? Secondly, is the effect indirect in that both cigarette smoking and ischemic heart disease mortality are related to a third and common factor?

Procedure: Data were obtained from 600 apparently healthy South African males aged 25 to 55 who were actively engaged in their occupations, concerning their income, occupation, smoking habits, and customary diet, with particular emphasis on items of food that contain fat, such as meat, dairy products, eggs, margarines, oils, etc. Anthropometric measurements were recorded and cholesterol chemically determined in the blood serum. Each racial group was divided into three income classes, but the economic scale is such that the high-income Bantu would overlap the economic level of the low- and medium-income Cape Colored, and the high-income Cape Colored would be on an economic par with the low-income European. Cigarette smokers were analyzed separately from pipe smokers and both were classified into heavy, medium and light smoking groups.

Findings: No relationship could be found between smoking and age, income, occupation, height, weight, or degree of obesity. The arterial pressures of heavy smokers tended to be slightly lower than those of non-smokers, but the differences were not significant. A highly consistent difference shown was the distribution of cholesterol between the alpha- and beta-lipoprotein fractions. This held true at each age range, for each race, and for each income sub-group. Such differences were paralleled by differences in the customary dietary fat intake, but these differences were not statistically significant.

These findings do not exclude the possibility that increased susceptibility to ischemic heart disease in heavy cigarette smokers could arise from the blood-pressure changes during smoking. On the other hand, the mechanism for the increased susceptibility of the smokers could operate via the changes in serum lipid found.

The first companion study showed that the taste thresholds for "bitter" were significantly higher in smokers than in non-smokers, while no differences appeared for sweet, sour, or salt. The age of the smoker, and thus presumably the duration and amount of smoking, both adversely affected the sensitivity to bitter tastes.

The second companion study showed that non-smokers prefer bland food and a fairly high proportion of smokers prefer salty and spiced food. Smokers consume more fat than non-smokers, but the differences are small. Heavy smokers consume significantly more meat and eggs than do non-smokers, and the latter consume more fat in the form of cakes, sweets and chocolate. These diet preferences may account for the differences in serum cholesterol levels that have been reported in surveys on smokers and non-smokers.

"BUERGER SYNDROME IN THE ORIENT." By Victor A. McKusick, M.D., and Willard S. Harris, M.D., Johns Hopkins University School of Medicine, Baltimore, Md. *The Lancet,* pages 1117-1118, May 20, 1961. (T.I.R.C. grantee: McKusick)

Purpose of study: The presumption that in the Orient the clinical and

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pathological picture is less obscured by a high frequency of atherosclerosis and thromboembolic disease than in Western countries prompted a study of the Buerger syndrome in Japan and Korea.

Procedures: Since early 1957 the Presbyterian Medical Center at Chonju, Korea, has admitted 62 patients with the diagnosis of Buerger's disease, all males; 28 of these who responded to letters were studied as was a control group of 28 Korean males. All but 5 of the 28 patients were farmers or farm workers whose diet consisted mainly of rice, pickled cabbage and other vegetables, soya-bean cake, and soya sauce. All were smokers, and most smoked heavily. Serum cholesterol and fasting blood sugar levels did not differ significantly from those of the controls. Visits to 6 medical centers in Japan revealed that most university medical services admit 10 to 15 patients annually with the Buerger syndrome. The age, sex, and social and economic status of the patients are essentially the same as in the Korean patients.

Findings: There appears to be in young males in the Orient a form of obliterative vascular disease which clinically and epidemiologically, and perhaps histologically, does not have the characteristics of atherosclerosis or multiple embolism. The etiology and pathogenesis may be complicated. That the essential lesion is an angiitis remains to be proved. Angiitis or not, the pathogenesis is not understood but appears to differ from that of other vascular diseases, particularly atherosclerosis.

Other grantor: U. S. Public Health Service.

"NORMAL RABBITS' AORTIC AND MYOCARDIAL CELLS GROWN IN VARIOUS CULTURE MEDIA." By T. Kokubu and O. J. Pollak, Dover Medical Research Center, Dover, Dell *Experimental Cell Research*, Vol. 24, pages 415-423, September 1961. (T.I.R.C. grantee: Pollak)

Purpose of study: In preparation for studies of the effects of tobacco derivatives on arterial and myocardial tissue cultures, it was necessary to establish optimal conditions for *in vitro* growth of vascular cells.

Procedure: Segments of ascending, thoracic and abdominal aorta and of heart papillary muscle were removed from adult rabbits as soon as possible after death, rinsed in sterile isotonic saline solution, and cut into pieces about one millimeter square. *In vitro* cultures were started within two hours. The fluid medium was changed twice a week. Microscopic observations were made every other day for about three weeks. Five separate nutrient media were tested.

Findings: Undifferentiated fibroblasts from heart grew best; cells from ascending aorta grew better than cells from thoracic or abdominal aorta. Rabbit serum promoted cell growth best; horse serum and human serum enhanced growth more than chicken serum. Cells grown in chicken serum differed morphologically from cells cultured in media with other serum additives. Growth in medium without any serum resembled closely the results obtained with chicken serum. For practical reasons, horse serum is suited best as additive to nutrient medium for *in vitro* cultures of rabbits' cardiovascular cells.

Other grantor: National Heart Institute.

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"CIRCULATORY EFFECTS OF PIPE AND CIGAR SMOKING." By David L. Simon, M.D., and Arnold Iglauer, M.D., University of Cincinnati College of Medicine, Cincinnati, O. *American Journal of Medical Sciences,* Vol. 241, pages 22-30, January 1961. (T.I.R.C. grantee: Simon)

Purpose of study: Much attention has been devoted to the effect of smoking cigarettes on the circulation but relatively little information has been available on the circulatory action of pipe and cigar smoking. Therefore, it was decided to gather data on the circulatory changes caused by smoking regular commercial and low nicotine cigars and pipe tobacco and to compare the results with other studies on cigarette smoking and chewing tobacco.

Procedures: A group of 25 habitual male smokers ranging from 21 to 69 years in age, of whom 15 smoked cigars and 10 smoked pipes, were studied during regular and sham smoking periods under identical conditions. Ballistocardiograms, blood pressure, pulse rates and skin temperatures were studied during and after the smoking periods.

Findings: The usual effects of tobacco smoking on the circulation were found (drop in skin temperature, increase in pulse and blood pressure), but were not as marked as those usually found following cigarette smoking or tobacco chewing. The incidence of changes in the ballistocardiograms was less than that found following chewing tobacco, but greater than that found following cigarette smoking. Circulatory changes were slightly less following low nicotine cigars and pipes when compared to standard cigars and pipes. Sham smoking did not produce circulatory changes.

"THE CIRCULATORY RESPONSE TO SMOKING: THE EFFECT OF SMALL DOSES OF HEXAMETHONIUM AND OF MEPHENTERMINE ON THE PATTERN OF RESPONSE." By Caroline Bedell Thomas, M.D., and Edmond A. Murphy, M.D., Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md. *Journal of Chronic Diseases,* Vol. 12, pages 534-543, November 1960. (T.I.R.C. grantee: Thomas)

Purpose of study: During a standard ballistocardiographic smoking test among healthy young adults, some subjects showed hyperreactivity of blood pressure, heart rate, or cardiac output in various combinations, while others with similar smoking habits showed little change or even a negative response. In order to investigate further these individual differences, it seemed worth while to attempt to change the response to smoking by modifying the physiologic state of the subjects with different pharmacologic substances.

Procedures: Observations were made on the circulatory response to smoking a single cigarette following small doses of hexamethonium, of mephentermine, or of placebo (isotonic sodium chloride solution), administered by intravenous injection. These substances were given in random order in a series of separate double blind tests. Seven healthy white male subjects had 8 tests apiece on different days, 3 with each of the active pharmacological preparations and 2 with the placebo. The aim was to produce minimal measurable effects. Since sensitivity varies from subject to subject, the appropriate dose had to be found by experiment.

Findings: After injection of the placebo, the average circulatory response

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to smoking one cigarette was similar to that in a larger series previously reported in which no injection was given. From the duplicate placebo tests an estimate of the average variability of these tests could be made.

Hexamethonium did not influence the mean response to smoking so far as could be judged by a paired comparison with the placebo tests. The heart rate was further (though not significantly) increased, and this might have been expected since both hexamethonium and smoking independently tend to increase the heart rate. When the mephentermine sulfate and placebo tests were compared, however, both the change in systolic pressure and in cardiac output after smoking were significantly altered by mephentermine. The other variables were not thus affected. The constancy within the individual of the measurements obtained after a cigarette is smoked, previously reported as the "ceiling phenomenon," is impaired but not entirely abolished by small doses of these drugs. In this respect the "ceiling phenomenon" resembles a cardiovascular homeostatic mechanism.

In conclusion it appears that this experimental approach reveals individual differences in homeostasis, but that these changes are not readily grouped. At present the results seem too various and too complex to permit a simple classification of subjects which could be used for screening purposes.

Other grantor: Veterans Administration.

"PATHOGENETIC INTERRELATIONS IN HYPERTENSION AND CORONARY ARTERY DISEASE." By Caroline Bedell Thomas, M.D., Johns Hopkins University School of Medicine, Baltimore, Md. *Diseases of the Nervous System*, Vol. 22, pages 39-45, April 1961.

Purpose of study: In a long-term prospective investigation of the precursors of hypertension and coronary disease, studies are being made of the occurrence, nature and interrelationship of certain genetic, physiological, metabolic and psychological characteristics in healthy Johns Hopkins medical students. They are being followed over the years to determine which factors or constellations of factors are most frequently associated with the early onset of disease. It is the author's hypothesis that multiple factors play a determining role in the etiology of these disorders. The exact form of disease and age of onset in a given individual is thought to depend on the nature and number of factors in his own genetic inheritance in combination with the particular environmental stresses encountered as he goes through life.

Procedures: The characteristics of 2 extreme groups of students were examined — those with 2 definitely affected parents and those whose parents are both free from hypertension, coronary disease, obesity and diabetes. Among 743 white male medical students observed in the first 12 classes studied, 13 gave a history of hypertension in both parents, 11 had a father with coronary disease and a mother with hypertension, and 3 reported that both parents had coronary disease. After determining that the traits under scrutiny were similarly distributed in these 3 small groups, the study was extended to the numerous factors differentiating them from the "normal" group.

Findings: The offspring of 2 parents affected with hypertension and/or coronary disease are significantly different in a number of ways from the

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offspring of 2 unaffected parents. On the average, they are 10 pounds heavier, more frequently have hypercholesteremia, have higher resting systolic blood pressure levels, and are more likely to be smokers. The offspring of 2 obese parents are distinguished for their own excessive weight and also have higher cholesterol levels.

The broad implications of these studies are that the offspring of different kinds of human matings have significantly different physiological, metabolic and psychological characteristics, that the differences usually are not great, but that they are compatible with the hypothesis of multifactorial inheritance. Also, the ability to predict high susceptibility to hypertension and/or coronary artery disease in a given individual may well depend upon the identification and appraisal of a constellation of factors rather than upon any single characteristic. When the prehypertensive or precoronary individual can be identified with precision, the prospects for the prevention of these disorders will be bright.

Other grantors: U. S. Public Health Service and Veterans Administration.

"CARDIOVASCULAR INTERACTION OF NICOTINE, ERGONOVINE, AND HYPERCHOLESTEROLEMIA IN THE RABBIT." By Duane G. Wenzel, Ph.D., James A. Turner, M.D., Scott W. Jordan, M.D., and Jasbir Singh, M.S., University of Kansas, Lawrence and Kansas City, Kan. *Circulation Research,* Vol. 9, pages 694-699, May 1961. (T.I.R.C. grantee: Wenzel)

Purpose of study: It is important to determine possible causes for the observed interaction of nicotine and a hypercholesterolemic diet in both the myocardial and the peripheral vascular effects encountered in rabbit experiments.

Procedure: An initial experiment employed 4 groups of 12 female albino New Zealand rabbits: an untreated control group; rabbits receiving 1.14 mg/Kg./day of nicotine in drinking water; rabbits receiving 1 percent cholesterol and 5 percent cottonseed oil in the diet; and a fourth group receiving nicotine and the cholesterol-cottonseed additives. Various circulatory and vascular readings were taken at intervals and compared to pretreatment levels. After 24 weeks the animals were sacrificed and the hearts and femoral arteries were examined. Because of the lack of marked micropathological changes in the cholesterol and nicotine-cholesterol hearts, additional groups of rabbits were tested with ergonovine injected because of its value in demonstrating alterations in the electro-cardiogram indicative of coronary disease.

Findings: Throughout the course of the initial experiment, the peripheral circulation was depressed, the systolic pressure elevated, and the coagulation rate speeded. Peripheral pathologic changes were minimal, and areas of cardiac necrosis observed in a similar previous study were absent. In order to determine the cause of this apparent discrepancy, a second group of rabbits was similarly treated except that ergonovine was added to the diet. The 24-week histological examination this time revealed cardiac necrosis in all animals receiving the combined nicotine-cholesterolergonovine treatment. This effect had not been obtained with either nicotine or cholesterol or with nicotine and cholesterol together.

Other grantor: University of Kansas General Research Fund.

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IV. *Psycho-Physiological Studies*

"CONSTITUTION AND SMOKING." By Albert Damon, M.D., Ph.D., Department of Epidemiology, Harvard School of Public Health, Boston. *Science*, pages 339-341, Aug. 4, 1961.

Purpose of study: The detection of determinants of tobacco smoking would help in understanding and possibly preventing diseases said to be associated with smoking. Since the use of tobacco may vary from one cultural group to another, it was considered desirable to study subjects with a common culture and a similar biological background, and who thus constitute a relatively homogeneous group.

Procedure: Such a group has been under investigation since 1956. In 1958 it comprised 167 male factory workers whose parents were born within 75 miles of Naples, Italy. Of the workers, 151 were born and raised near Boston, Mass., and the other 16 near Naples, 7 coming to the U. S. before the age of 10 and 9 when they were 10 or older. Smoking habits were graded in 5 categories: never smoked, rare or occasional smokers, moderate smokers, heavy smokers, and very heavy smokers: more than 30 cigarettes or 10 cigars or pipes daily. Standard techniques were followed for anthropometry, for somatotyping, and for serum cholesterol and blood pressure determinations. Dietary data were obtained through a 45-minute interview, etc., and activity was graded in 5 categories based on estimated exertion both on and off the job.

Findings: The results show a consistent and statistically significant tendency for lean men to smoke more than stout or fat (but not muscular) men. This association was not the result of different diets, since smoking and caloric intake as well as intake of component foods were independent of each other. The present findings confirm reports by others of slightly higher serum cholesterol among smokers. Contrary to previous findings, smokers in this series were no less masculine in physique, were no more active, and consumed no more alcohol than non-smokers.

"SOME HARVARD MEN AND THE SMOKING HABIT." By Carl C. Seltzer, Ph.D., Peabody Museum, Harvard University, Cambridge, Mass. *Harvard Alumni Bulletin*, Feb. 4, 1961.

As part of a more intensive study of related biological factors in tobacco smoking by Harvard men, a survey was made of the smoking habits of the class of 1946 through questionnaire, to which 927, or 81.4 percent of the members, responded. Twenty-five percent were classified as non-smokers, compared to 18 percent in the U. S. population; 59 percent were current regular smokers; and 16 percent were former regular smokers who discontinued the habit for various reasons, about the same as the national average.

While 18 percent of the regular smokers in the U. S. started smoking before their sixteenth birthday, only 3 percent of the Harvard men started so early. The average smoking history of current smokers was 15.6 years, while the average duration of smoking for the ex-smokers was 11.4 years.

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suggesting that the period 1954-55 was the time in which many smokers "broke the habit."

Among current smokers, 60.2 percent smoke cigarettes only, 12 percent cigarettes and pipe, 5.9 percent cigarettes and cigars, and 2.8 percent all three tobacco forms; 9.4 percent smoke pipe only, 5.9 percent cigars only, and 3.9 percent cigars and pipe. For the U. S., cigarette only smokers comprise 76.3 percent of all smokers and combined cigarettes and other forms of smoking total 94 percent.

The Harvard men are also heavier smokers than the national average: 9 percent of the cigarette smokers consume over 2 packs daily, against 3 percent for the U. S.: 46 percent consume between 1 and 2 packs daily, against 27 percent for the U. S.

The Harvard smokers tend to be found more frequently in the field of business contacts and administration, editors, educators, and museum curators, etc., whereas there are proportionally more non-smokers among engineers, surgeons, clergymen, teachers, and librarians. The pipe smokers are more frequently found among research scientists, cultural administrators, lawyers, college professors, and school teachers.

V. *Tobacco Chemistry and Biochemistry*

"BIOSYNTHESIS OF ANABASINE AND OF NICOTINE BY EXCISED ROOT CULTURES OF NICOTIANA GLAUCA." By Marie L. Solt, R. F. Dawson, and D. R. Christman, Department of Botany, Columbia University, New York, N. Y., and Brookhaven National Laboratory, Upton, N. Y. *Plant Physiology,* Vol. 35, pages 887-894, November 1960. (T.I.R.C. grantee: Dawson)

"THE BIOSYNTHESIS OF NICOTINE FROM NICOTINIC ACID: CHEMICAL AND RADIOCHEMICAL YIELDS." By R. F. Dawson, D. R. Christman, M. L. Solt, and A. P. Wolf, Department of Botany, Columbia University, New York, N. Y., and Brookhaven National Laboratory, Upton, N. Y. *Archives of Biochemistry and Biophysics,* Vol. 91, pages 144-150, November 1960.

"BIOSYNTHESIS OF THE NICOTIANA ALKALOIDS." By R. F. Dawson, Department of Botany, Columbia University, New York, N. Y. *American Scientist,* Vol. 48, pages 321-340, September 1960.

Isotopic tracers applied to the study of tobacco alkaloid biosynthesis have revealed that nicotinic acid is a common precursor of nicotine and anabasine. Nicotinic acid contributes the pyridine ring to each alkaloid, while ornithine and lysine contribute the pyrrolidine and piperidine rings, respectively.

Nicotinic acid is probably reduced 1-6 prior to combining with the precursors of the pyrrolidine and piperidine moeities. This conclusion is supported by the fact that hydrogen-isotope label on the pyridine ring of nicotinic acid is transferred *in situ* to the pyridine ring of nicotine from all positions on the pyridine ring except number 6. The occurrence of the postulated 1,6 dihydro intermediate helps to explain the otherwise chemically difficult displacement of the carboxyl group of nicotine acid. There is

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no indication in these experiments of the nature of the circumstances which compel the plant to synthesize apparently terminal products from such metabolically useful intermediates.

One of the impressive aspects of alkaloid biosynthesis by the excised root cultures of *N. tabacum* and *N. glauca* is the extraordinary rate stability of the process. In our experience, alkaloid production rate is a clonal (i.e. inherited) character and is not subject to ready modification by the usual components of root culture environment. Of particular interest in this connection is the failure of added precursors such as nicotine acid, either alone or with lysine or with ornithine, to increase significantly the yields of anabasine or of nicotine.

The biosynthetic apparatus for nicotine and for anabasine are considered to be separated into two distinct compartments in the excised root, namely the growing root tip and the matured root axis. However, the problem of explaining rate stability within compartments still remains. At present, it seems well to adopt as a working hypothesis the prospect of a common rate-limiting step for both growth and nicotine production.

Other grantors: University of Missouri, Princeton University, Columbia University, Rockefeller Foundation, U. S. Atomic Energy Commission, and The American Tobacco Company.

"THE GIBBERELLIC ACID INHIBITION OF NICOTINE BIOSYNTHESIS." By M. L. Solt, R. F. Dawson, and D. H. Christman, Department of Botany, Columbia University, New York, N. Y., and Brookhaven National Laboratory, Upton, N. Y. *Tobacco Science,* Vol. 5, pages 95-98, Sept. 8, 1961.

Purpose of study: E. V. Parups (1959-1960) has shown that the reduced nicotine content of tobacco plants treated with gibberellic acid is due to a reduced rate of synthesis and not to an accelerated destruction of nicotine in the plant body. The authors have shown that the biosynthesis of nicotine possesses not only substantial rate stability but also a rate dependency on growth. It would be experimentally advantageous if gibberellic acid were effective in altering these rate relationships.

Procedures: Excised root cultures of *Nicotiana tabacum L.* var. Turkish were treated with gibberellic acid and labeled nicotine precursors, nicotinic acid and ornithine, were added to the cultures. After harvesting, both the dried root tissue and the concentrated spent culture solution were extracted, and the nicotine so obtained was assayed for radiocativity by standard procedures.

Findings: Addition of gibberellic acid to the culture medium 29 days before harvest produced a marked reduction of nicotine output, the maximum effect of about 50 percent being obtained at a concentration of 1 ppm gibberellic acid. Similar effects were obtained by adding the equivalent of 5 ppm at each of several five-day intervals during the culture passage. The presence of gibberellic acid was not associated with an accelerated rate of destruction of added labeled nicotine. When labeled nicotinic acid or labeled ornithine was supplied to the cultures with and without gibberellic acid, the results were qualitively the same; nicotine yield was again reduced up to 50 percent by gibberellic acid, but the reduction in yield occurred largely at the

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expense of endogenous precursors. These results show that the inhibitory action of gibberellic acid on nicotine biosynthesis very likely occurs at three different points in the metabolic sequence.

Other grantor: U. S. Atomic Energy Commission.

"DETERMINATION OF ARSENIC IN FLUE-CURED TOBACCO AND IN SOILS." By H. G. Small Jr. and C. B. McCants, Department of Soils, North Carolina Agricultural Experiment Station, Raleigh. *Soil Science Society of America Proceedings,* Vol. 25, pages 346-348, September-October 1961. (T.I.R.C. grantee: McCants)

Procedures are described for the semimicro analysis for arsenic in flue-cured tobacco and in soils. The plant material is digested with a mixture of nitric, sulfuric and perchloric acids and the soil with sulfuric and perchloric acids. Arsenic is distilled directly from the digestion flask, absorbed in an iodine solution and determined colorimetrically by the moylbdenum-blue method.

The data show that good recovery of arsenic and reproducibility of results were obtained. The acid digestion method for plant material gave results closely comparable to those obtained by oxidation in an oxygen bomb. The evidence from soils indicates that the digestion and distillation procedure employed removed substantially all of the arsenic.

The evidence presented suggests quite strongly that with wet-digestion procedures, results can be obtained that are equally as reliable as those from the bomb combustion method.

"MAMMALIAN DEGRADATION OF (-)-NICOTINE TO 3-PYRIDYL-ACETIC ACID AND OTHER COMPOUNDS, by Herbert McKennis Jr., Edward R. Bowman, and Lennox B. Turnbull, Department of Pharmacology, Medical College of Virginia, Richmond. *Proceedings, Society for Experimental Biology and Medicine,* Vol. 107, pages 145-148, May 1961. (T.I.R.C. grantee: McKennis)

Purpose of study: Research by the authors and others has led to the identification of a wider complexity in the metabolism of nicotine than was estimated only three years before. It was decided to investigate further the metabolism of randomly labeled (-)-nicotine-C^{14} in order to ascertain the sequence of metabolic reactions.

Procedure: Randomly-labeled (-)-nicotine-C^{14} was administered intravenously to two mongrel dogs over an 8-hour period at a dosage of 4.25 mg./kg. Urine was collected from the bladder by an indwelling cathether during infusion and a subsequent 19-hour period. Radioactive determinations were made and chromatograms prepared. In a companion study (-)-cotinine was administered orally to a third dog.

Findings: 1. The pattern of urinary excretion of C^{14} in the dog following intravenous administration of (-) nicotine-C^{14} was examined chromatographically by improved procedures. 2. The fractionated urine showed C^{14} activity corresponding chromatographically to the known metabolites: cotinine, gamma-(3-pyridyl)-gamma-methylaminobutyric acid, desmethyl-cotinine-hydroxycotinine, and gamma-(3-pyridyl)-beta-oxo-N-methylbutyramide. 3. Among many unidentified radioactive components, the urine contained material corresponding chromatographically to 3-pyridylacetic acid.

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4. Following oral administration of (-)-cotinine, 3-pyridylacetic acid was isolated from urine and characterized by analysis, melting point, mixed melting point and as its picric acid salt. 5. A precursor of 3-pyridylacetic acid is, on formal grounds, gamma-(3-pyridyl)-beta-oxybutyric acid, derivable from the known metabolite gamma-(3-pyridyl)-beta-oxo-N-methylbutyramide.

Other grantor: The American Tobacco Company.

"DEMETHYLATION IN THE METABOLISM OF (-)-NICOTINE *IN VIVO*." By Herbert McKennis, Jr., Einosuke Wada, Edward R. Bowman and Lennox B. Turnbull, Department of Pharmacology, Medical College of Virginia, Richmond. *Nature*, pages 910-911. June 3, 1961.

Purpose of study: Discrepancies existed among previous studies of the physiological disposition of nicotine randomly labeled with carbon-14. Several workers found no radioactive carbon dioxide in expired air of mice and dogs after intravenous administration of the labeled nicotine, contrary to previous work by the Virginia scientists which indicated that metabolism of nicotine involves degradation to single-carbon metabolites. To resolve the apparent contradiction, labelled nicotine containing a high level of activity in the methyl group was employed.

Procedure: Male albino rats received intraperitoneally a synthesized nicotine-methyl-C^{14}, and expired carbon dioxide was collected in sodium hydroxide traps and then precipitated as barium carbonate.

Findings: During the first 6-hour period after administration of the nicotine, the respiratory carbon dioxide from 3 rats contained an average of 5.7 percent of the administered radioactivity, with individual values 7.5, 4.0 and 5.6 percent. Further elimination in a subsequent 18-hour period gave cumulative values of 12.8, 6.2 and 8.4 percent of the administered dose. In addition, a small but significant amount of carbon-14 activity was present as urea in the individual 24-hour urines, as determined from carbon dioxide evolved by urease. Since the radioactivity of randomly labeled nicotine-C^{14} is excreted to the extent of 94 percent in the urine of rats, the addition of carbon-14 determined by carbon dioxide in these studies gives a total elimination approaching 100 percent. This provides convincing evidence that, after single doses, storage of nicotine or its metabolites occurs to only an extremely limited extent. The results point to the importance of single-carbon compounds in the metabolism of nicotine in the rat.

Other grantor: The American Tobacco Company.

"NORCOTININE (DESMETHYLCOTININE) AS A URINARY METABOLITE OF NORNICOTINE." By Einosuke Wada, Edward R. Bowman, Lennox B. Turnbull, and Herbert McKennis, Jr., Department of Pharmacology, Medical College of Virginia, Richmond. *Journal of Medicinal and Pharmaceutical Chemistry*, Vol. 4, pages 21-30, July 1961.

Following intravenous administration of (-)-nornicotine, the dog excretes in the urine a variety of Koenig-positive compounds. A chloroform extract of the alkalinized urine contained norcotinine, nornicotine, and other components. The aqueous phase remaining from the chloroform extract contained gamma-(3-pyridil)-gamma-aminobutyric acid, which was metamized to (-)-norcotinine (2-(3-pyridil)-pyrrolidone-5). Reduction of

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optically active norcotinine with lithium aluminum hydride resulted in the formation of a mixture of optically active and optically inactive nornicotine.

"THE ABSORPTION OF NICOTINE FROM THE URINARY BLADDER OF THE DOG." By Joseph F. Borzelleca, Department of Pharmacology, Medical College of Virginia, Richmond. *Archives Internationales de Pharmacodynamie,* Vol. 133, pages 444-451, Oct. 1961. (T.I.R.C. grantee: Herbert McKennis Jr., Medical College of Virginia)

Purpose of study: There is an apparent inconsistency in the findings of several authors as to the relative excretion and absorption of nicotine, reported in laboratory studies with dogs and cats, which requires resolution. Since bladder reabsorption of nicotine might have a bearing on the toxicological effects of nicotine and other substances it was decided to reinvestigate the absorption of nicotine from the bladder of the dog.

Procedures: Adult mongrel dogs of both sexes were anesthetized and carotid blood pressure, respiration, electrocardiograms, and urine outflow were recorded. The bladder was drained and cleansed by a catheter, through which solutions were instilled or outflow during perfusion occurred. After appropriate intravenous test doses to determine the responsiveness of the animals, a 20 mg/ml solution of nicotine in an appropriate buffer was perfused through the bladder at a rate of 1.5 ml/minute. The pH of the perfusing fluid from the bladder did not change more than 0.2 pH unit during the experimental period.

Findings: The absorption of nicotine from the bladders of the dogs was demonstrated. There was no significant difference between the sexes. The physiological changes taken as an indication of nicotine absorption were changes in blood pressure, respiration, and urinary outflow. Within the pH range investigated the rate of absorption appeared to be dependent upon the pH of the nicotine solution.

Other grantors: U.S. Public Health Service and The American Tobacco Company.

"THE BACTERIAL OXIDATION OF NICOTINE. IV. THE ISOLATION AND IDENTIFICATION OF 2,6-DIHYDROXY-*N*-METHYLMYOSMINE." and "V. IDENTIFICATION OF 2,6-DIHYDROXYPSEUDOOXYNICOTINE AS THE THIRD OXIDATIVE PRODUCT." By S. H. Richardson and Sydney C. Rittenberg, Department of Bacteriology, University of Southern California, Los Angeles. *Journal of Biological Chemistry,* Vol. 236, pages 959-964 and 964-967, March 1961. (T.I.R.C. grantee: Rittenberg).

Purpose of study: Previous studies in this series have established 6-hydroxynicotine and 6-hydroxypseudooxynicotine as the first and second oxidative products of nicotine metabolism by a soil bacterium. These studies were undertaken to clarify the subsequent metabolic transformations of nicotine and to identify the third oxidative product.

Procedures: The oxidation of nicotine, 6-hydroxynicotine and 6-hydroxypseudooxynicotine by appropriate enzyme fractions was studied manometrically and spectrophotometrically. The product formed by the three, two, or one step oxidation, respectively, of these substrates was synthesized enzymatically and isolated in crystaline form.

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Findings: The isolated compound was identified as 2,6-dihydroxy-*N*-methylmyosmine on the basis of its chemical properties and its elemental analysis. The compound was not further metabolized and appears to be a side product on the main pathway of nicotine degradation by the bacterium employed. The true third oxidative product was identified as 2,6-dihydroxy-pseudooxynicotine which, in the presence of the proper enzyme fraction, is further metabolized; otherwise it is converted non-oxidatively and non-enzymatically to the metabolically inactive 2,6-dihydroxy-*N*-methylmyosmine, the compound previously isolated.

"PAPER CHROMATOGRAPHIC DETERMINATION OF RUTIN IN TOBACCO." By C. H. Yang, W. Chorney, W. Dunlap, E. L. Murphy, Y. Nakagawa, N. Scully, R. Watanabe and S. Wender, Chemistry Department, University of Oklahoma, Norman, and Medical Research, Argonne National Laboratory, Argonne, Ill. *Tobacco Science,* Vol. 4, pages 238-242, Dec. 23, 1960. (T.I.R.C. grantee: Wender)

Procedures which use the aluminum chloride or boric acid-citric acid reagents, but do not separate the rutin from other flavonol glycosides or from chlorogenic acid and related depsides or other possible interfering substances, may not be accurate for quantitative analysis of rutin in many tobacco samples. Three chromatographic methods developed for determination of the rutin in tobacco are described in detail. Experiments involving addition of known quantities of rutin to a tobacco extract before chromatography usually gave 95 percent or better recovery of the added rutin after its passage through the analytical procedure.

Other grantor: U. S. Atomic Energy Commission.

VI. *Other Studies*

"SOME EVIDENCE FOR A MECHANICAL RECEPTOR IN OLFACTORY FUNCTION." By Showa Ueki, Faculty of Medicine, University of Kyushu, Japan, and Edward F. Domino, Department of Pharmacology, University of Michigan, Ann Arbor. *Journal of Neurophysiology,* Vol. 24, pages 12-25, January 1961. (T.I.R.C. grantee: Domino)

Purpose of study: In certain fish the olfactory organs are sensitive to mechanical as well as chemical stimuli, whereas in mammals there is an absence of conclusive evidence for a mechanical receptor in olfactory function. This study was undertaken in an attempt to provide some evidence for such a hypothesis.

Procedure: Electrodes were implanted surgically in anesthetized dogs and monkeys in various neocortical and rhinencephalic structures including the olfactory bulb, amygdala, and hippocampus. One month later various gases and odoriferous substances were applied through a glass cannula inserted into the nose, and electrical "bursts" in the various olfactory structures were recorded.

Findings: Waves of 20 to 40 c./sec. were recorded synchronous with inspiration in the monkey and with inspiration and expiration in dogs. The phenomena were predominantly ipsilateral. Electrical activity of similar frequencies could be elicited by blowing room air, various gases and solutions

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into the nostril. It appeared that a mechanical component was involved in these phenomena. Therefore studies in acute dogs given local anesthesia and placed on artificial respiration were undertaken. Evidence was obtained that in about 50 percent of the dogs electrical discharges were recorded in the olfactory bulb to odor-free oxygen, nitrogen, and carbon dioxide, and were dependent upon the velocity of gas flow. The areas in the olfactory bulb where mechanical responses were obtained were relatively few compared to those areas responding to odors. In all the animals studied the electrical responses to all odors including tobacco smoke were enhanced with increasing flows of oxygen when the flow of the material was kept constant. Thus the concentration of odor per unit volume of gas was actually decreased at a time when the olfactory bulb responses were markedly enhanced.

It is concluded that preliminary evidence has been obtained for the existence of a mechanical receptor in olfactory function. It is hypothesized that one of the reasons tobacco smoke is so effective in stimulating olfactory bulb discharge is that its smoke particles are small enough to mechanically as well as chemically bombard the olfactory receptors.

"EFFECTS OF MECAMYLAMINE ON THE GOLGI RECURRENT COLLATERAL-RENSHAW-CELL SYNAPSE IN THE SPINAL CORD." By S. Ueki, University of Kyushu, Japan, K. Koketsu, Department of Psychiatry, and E. F. Domino, Department of Pharmacology, University of Michigan, Ann Arbor. *Experimental Neurology,* Vol. 3, pages 141-148, February 1961.

Purpose of study: The fact that mecamylamine is a secondary amine with "nicotinic" blocking properties suggested that it would act at the Golgi recurrent collateral-Renshaw-cell synapse in the spinal cord. The experiment was designed to test this hypothesis.

Procedure: Twenty-one adult cats of both sexes were anesthetized, and the spinal cord was exposed surgically and prepared for electrical stimulation. A glass micropipette was introduced into the Renshaw-cell interneuron pool, and electrical activity of the cells was recorded. All drugs were administered intravenously.

Findings: Antidromic stimulation of the ventral roots produced extracellular discharges of the Renshaw-cells for variable periods of time. Minimal to no spontaneous activity was recorded. The principal effect of mecamylamine was to decrease the terminal discharges of the Renshaw cell to antidromic stimulation. No elaborate statistical analysis of the effects was undertaken. Not only could mecamylamine alone reduce the activity of Renshaw cells that were fired antidromically, but it would also block the action of nicotine and physostigmine. Nicotine was very effective in stimulating Renshaw cells directly. The effectiveness of mecamylamine to depress the Golgi collateral-Renshaw-cell synapse is additional pharmacological evidence that this is a "nicotinic"-type cholinergic synapse in the central nervous system.

Other grantor: U. S. Public Health Service.

"CHANGING CONCEPTS OF THE ROLE OF TOBACCO IN THE MANAGEMENT OF DISEASE." By Paul S. Larson, Ph.D., Harvey B.

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Haag, M.D., and Herbert Silvette, Ph.D., Medical College of Virginia, Richmond. *American Journal of the Medical Sciences,* Vol. 240, pages 613-635, November 1960. (T.I.R.C. grantee: Haag)

For almost as long as people have been using tobacco, writers have been speculating on its role in the genesis of disease. Except for a few genuinely tobaccogenic diseases (of which the most unequivocal is tobacco allergy), the etiological role of tobacco is just as obscure today as, say, a century ago; but a survey of a considerable sample of the clinical tobacco literature of the past 50 years has revealed a significant change in opinion regarding the place of tobacco in the management of certain diseases. This latter is independent of speculation or opinion regarding tobacco etiology. Thus, there is no perceptible agreement among clinicians concerning the role of tobacco in the etiology of thromboangiitis obliterans, but there is unanimity that tobacco exerts a harmful influence once the disease is established, and should therefore be strictly forbidden patients with this condition.

The present paper is concerned only with tobacco-use in the management of certain diseases: tobacco allergy, angina, and amblyopia; cardiovascular diseases; chronic bronchitis, pulmonary emphysema, and pulmonary tuberculosis; and peptic ulcer. It is emphasized that, with the perhaps sole exceptions of tobacco allergies and nicotine hypersensitiveness, the observed influence of tobacco or tobacco-smoking on the course of any disease affords no valid information concerning its etiology. One may venture to generalize that, where once smoking was categorically forbidden in many diseases, it is now permitted in moderation by competent authorities.

The main conclusions to be drawn from this survey are clear enough. In the case of specific tobaccogenic diseases properly diagnosed, the *cause* of the disease, by definition, tobacco, may be forbidden without doubts and should be prohibited without equivocation. If one defines a non-tobaccogenic disease as one which occurs indistinguishably in both tobacco users and non-users, regardless of its respective incidence-rates, then it may be concluded that there *is* nothing better than abstention from tobacco, though sometimes there *may be* something worse: emotional disturbances of one sort or another, or the substitution of an even less desirable habit (for example, over-eating) for that of moderate tobacco-smoking. The fairly recent realization of physicians that the "psychic" good effects of tobacco-smoking might outweigh its "somatic" harm, represents the "changing concept" of the title.

"SOME EFFECTS OF NICOTINE AND SMOKING ON METABOLIC FUNCTIONS." By P. S. Larson, Ph.D., H. B. Haag, M.D., and H. Silvette, Ph.D., Department of Pharmacology, Medical College of Virginia, Richmond. *Clinical Pharmacology and Therapeutics*, Vol. 2, pages 80-109, January-February 1961.

A survey of medical and scientific literature on the metabolic effects of tobacco has drawn attention to the relative deficiency in this area of investigation, and the need to study the effects of nicotine using concentrations that include those encountered in man. Studies show that nicotine appears capable of increasing heat production, oxygen consumption, metabolic rate, and blood sugar. The effect on serum cholesterol and lipoprotein levels is not yet clear. Generally, the levels appear to be higher in smokers than in non-smokers, but the reason for the difference is obscure. It is inter-

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esting to note that there are few clinical reports which implicate nicotine or tobacco smoke etiologically or otherwise in deficiency or metabolic disorders.

So potent a drug as nicotine can be made to have an influence on metabolism, whether in the intact organism, individual organs, tissues, cells, or cellular components — when used in sufficient quantity. It may be emphasized that it is the concentration of nicotine obtaining in the cells or intracellular fluid of normal smokers which alone carries any validity in assessing the effects of tobacco smoking.

"Experimental" concentrations of nicotine must be matched to those "normally" occurring in tissues and body fluids of smokers. Only such concentrations can elucidate the pharmacologic aspects of tobacco smoking: concentration many times these express only the toxicologic characteristics of nicotine. If toxic doses or concentrations of nicotine have no demonstrable effect on metabolic or other activities, this negative evidence is very probably valid with respect to tobacco smoking; whereas the converse is, equally probably, far from true. It is never a work of supererogation to repeat that tobacco smoking, as it is performed by the smoking millions, is pharmacologic, and only very rarely indeed a toxicologic phenomenon.

"ACTION OF NICOTINE AND TOBACCO-SMOKING ON THE ADRENAL MEDULLA." By H. Silvette, Ph.D., P. S. Larson, Ph.D., and H. B. Haag, M.D., Department of Pharmacology, Medical College of Virginia, Richmond. *Archives of Internal Medicine*, Vol. 107, pages 915-931, June 1961.

A review of the extensive literature on the systemic effects of nicotine and smoking shows that both may stimulate epinephrine release from the adrenals, either directly or reflexly. Endogenous epinephrine and levarterenol exert a wide variety of effects in the body, but epinephrine release from the adrenals remains on the whole an emergency "fight or flight" mechanism. The studies show that this effect of nicotine or smoking affects or effects many body functions, relatively trivial (e.g. blood sugar rise) or relatively important (e.g. vasoconstriction).

So far as smoking by man is concerned, these findings raise two questions. First: Is the dose of nicotine derived from smoking sufficient to activate the epinephrine-release mechanism, directly or indirectly? The answer appears to be a rather hesitant affirmative.

Second: If so, is a repetitive stimulation of the epinephrine-release mechanism, and subsequently of epinephrine "shock organs" (particularly the cardiovascular system), of any long-term consequence to the habitual smoker? The answer to this question is still unknown.

On the whole, very few clinicians have elected to advance this particular mechanism to explain the effects of smoking on either the genesis or course of cardiovascular disease — or, in fact, of other diseases as well — in smokers.

"HEPATITIS — A FEATURE OF PERIODIC PERITONITIS." By Hobart A. Reimann, M.D., Hahnemann Medical College and Hospital, Philadelphia. *Journal of the American Medical Association*, Vol. 178, pages 334-335, Oct. 21, 1961.

Hepatitis occurred in two patients during episodes of periodic peritonitis, and overt and inapparent jaundice, hepatomegaly and splenomegaly

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were observed in three others. It is suggested that similar involvement may occur in other victims of periodic peritonitis. Hepatic involvement in periodic peritonitis raises two matters for speculation: Has it a bearing on lipid metabolism, to account for the effect of a diet low in fat that reduces the severity and frequency of symptoms in some victims? And, does the accumulation of plasmacytes and other cells in the liver, serosa, and elsewhere play a role in hyperglobulinemia that usually is present in periodic peritonitis, and the resultant development of amyloidosis?

"CANCER OF THE LUNG 1930 TO 1960: A REVIEW." By R. H. Rigdon and Helen Kirchoff, Department of Pathology, University of Texas Medical Branch, Galveston. *Texas Reports on Biology and Medicine,* Vol. 19, pages 465-513, Fall 1961. (T.I.R.C. grantee: Rigdon)

Introducing this review of 455 scientific papers on cancer of the lung, the authors say more has been written about this disease in scientific literature and the lay press than any other neoplastic disease. The question — Is cancer of the lung actually on the increase, and if so to what extent? — remains unanswered. It is not difficult to understand the confusion when we remember that the basic data on mortality incidence comes from death certificates. It was 1933 before we had nation-wide death reporting in the United States and 1939 before bronchogenic carcinoma was listed as such on our vital statistics. Regardless of whether the increase is only apparent or real, in 1960 cancer of the lung ranked first as the cause of death from cancer among men.

The role of smoking in lung cancer, although suggested before 1900, continued to be the burning question between 1930 and 1960. The hypothesis that smoking causes lung cancer is largely based on studies comparing the smoking habits of patients with other diseases or of healthy people and on studies in which the causes of death are compared in groups of people whose smoking habits have previously been established. Obviously from this review it is evident that the etiology and the pathogenesis of pulmonary cancer in man is not known.

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Recipients of Grants

Following is a list of all recipients of grants approved by the Scientific Advisory Board since initial grants were made in late 1954. It should be noted that some of the projects have been completed.

GRANTEE AND INSTITUTION	PROJECT TITLE *("C" indicates project completed; "P" indicates a report has been published by the grantee)*
CLARENCE M. AGRESS, M.D., *Chief, Cardiovascular Laboratory*, Veterans Administration Center, Los Angeles, Cal.	Measurement of the functional status of the human heart by frequency spectrum analysis of its vibrational energy
D. MURRAY ANGEVINE, M.D., *Professor of Pathology*, University of Wisconsin Medical School, Madison, Wis.	Pathologic—anatomic study of cellular changes in human bronchi (C)
STEPHEN M. AYRES, M.D., *Director of Research, Department of Pulmonary Physiology*, Saint Michaels Hospital, Newark, N. J.	Measurement of alveolar-arterial nitrogen difference by gas chromatography
FREDERICK W. BARNES, JR., M.D., PH.D., *Associate Professor of Medicine and Physiological Chemistry*, Johns Hopkins University School of Medicine, Baltimore, Md.	The role of hyperplasia in tissue response to chronic damage (C—P)
RALPH S. BECKER, PH.D., *Associate Professor of Chemistry*, University of Houston, Houston, Tex.	An investigation of the spectral and chromatographic characteristics of aromatic hydrocarbons
SAMUEL BELLET, M.D., *Director, Division of Cardiology*, Philadelphia General Hospital, Philadelphia, Pa.	The effect of nicotine on cardiac irritation in the presence of reserpine, and the effect of nicotine on coronary blood flow of dogs with coronary insufficiency (C—P) Effects of nicotine on the morphology of coronary arteries and aorta; fibrinolytic effects of nicotine on human and animal plasma; effects of cessation of smoking on serum cholesterol levels of chronic smokers
RICHARD J. BING, M.D., *Professor of Medicine and Chairman, Department of Medicine*, Wayne State University College of Medicine, Detroit, Mich.	The effect of smoking on the coronary blood flow and certain phases of myocardial metabolism in patients with arteriosclerotic or hypertensive cardiovascular disease (P) Studies in cellular physiology of heart muscle (P) Measurement of coronary blood flow by means of radioactivated albumin The effect of smoking on coronary blood flow in patients with arteriosclerotic heart disease and the effect of nicotine on storage of amines in heart muscle (P)

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GRANTEE AND INSTITUTION	PROJECT TITLE
	Measurement of coronary blood flow with a system using coincidence counting; the effect of nicotine and change in heart rate on cardiac metabolism and related subjects
FRED G. BOCK, M.S., PH.D., *Senior Cancer Research Scientist*, Roswell Park Memorial Institute, Biological Station, Springville, N. Y. (see Moore)	Investigation of the biological effects of cigarette smoke (C—P)
JAMES F. BONNER, PH.D., *Professor of Biology*, California Institute of Technology, Pasadena, Cal.	Enzymatic study of methylation reactions in plant tissue (C—P)
TOM G. BOWERY, PH.D., *Pesticide Residue Laboratory, Chemistry Department*, North Carolina State College, Raleigh.	TDE and endrin residues in cigarette smoke (C—P)
JOSEF BROZEK, PH.D., *Professor and Chairman, Department of Psychology*, Lehigh University, Bethlehem, Pa.	Biological characteristics of men and their smoking habits (C—P)
F. M. BUTT, M.D., *Professor of Pathology*, University of Southern California School of Medicine; *Chief Pathologist*, Los Angeles County Hospital, Los Angeles	Pathologic—anatomic study of cellular changes in human bronchi (C) Study of trace metal storage of pulmonary and liver tissue by spectographic and chemical methods (C)
RICHARD U. BYERRUM, PH.D., *Professor of Chemistry*, Michigan State University, East Lansing	Biosynthesis of the pyridine ring of nicotine (P)
SISTER M. EMILY CAHILL, PH.D., *Chairman, Chemistry Department*, Regis College, Weston, Mass.	Comparison of analytical methods by determining the percent recovery of arsenic added at known levels to tobacco samples and a broad survey of the amount of arsenic present in tobacco samples from a wide variety of sources
WILLIAM H. CARNES, M.D., *Professor of Pathology*, University of Utah College of Medicine, Salt Lake City.	Pathologic—anatomic study of cellular changes in human bronchi (C)
LEOPOLD CERECEDO, PH.D., *Professor of Biochemistry and Nutrition*, University of Puerto Rico, School of Medicine, San Juan (formerly Professor of Biochemistry, Fordham University, New York, N. Y.)	A study of early chemical changes in the lungs of tumor-bearing rats and mice (C—P)
HANS T. CLARKE, D.Sc., *Professor of Biochemistry*, Columbia University College of Physicians and Surgeons, New York, N. Y. (retired, see Gottschall)	Proteolytic activities of the white blood cells of men and the effect on white blood cell activities of carcinogens, nutrition and other influences (C)
JAY D. COFFMAN, M.D., *Instructor in Medicine*, Massachusetts Memorial Hospitals, Boston.	The effect of tobacco smoking on nutritive skeletal muscle blood flow as determined by the radioisotope disappearance technique

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GRANTEE AND INSTITUTION	PROJECT TITLE
JULIUS H. COMROE, JR., M.D., *Director, Cardiovascular Research Institute*, University of California Medical Center, San Francisco.	The effect of smoking upon airway resistance (C—P) Analysis of case histories on emphysema
DEAN M. CONNORS, M.D., *Associate Director, Department of Laboratory Medicine*, St. Mary's Hospital, Madison, Wis.	A study of the alterations in the human bronchial wall occuring with aging, with particular emphasis on elastic tissue changes and associated changes in the bronchial lumen size
PHILIP COOPER, M.D., *Chief, Surgical Service*, Veterans Administration Hospital, Bronx, N. Y.; *Clinical Professor of Surgery*, Albert Einstein Medical College, Bronx.	A study of the effects of cigarette smoking on levels of gastric acid, pepsin and uropepsin (C—P) A study of the effect of extracts of tobacco on cultures of tumor and normal cells. Animal transplants of tumor tissue from tissue cultures (P) Study of combined effect of injected viral agents and environmental factors, including carcinogens and tobacco smoke, on the tracheobronchial tree and pulmonary parenchyma of experimental animals and on tissues in organ culture
ALBERT DAMON, M.D., PH.D., *Assistant Professor of Medical Anthropology, Department of Industrial Hygiene*, Harvard School of Public Health, Boston, Mass.	Body form, smoking, and alcohol consumption among Italian-American men (C—P)
R. F. DAWSON, PH.D., *Professor of Botany*, Columbia University, New York, N. Y.	An investigation of the metabolism of pyridine compounds in the tobacco plant (C—P)
ANDREW S. DIBNER, PH.D., *Executive, Psycho-Research*, The Age Center of New England, Inc., Boston, Mass. (see Whiskin)	Psychological and behavioral characteristics of inhalers among smokers (C)
EDWARD F. DOMINO, M.D., *Associate Professor of Pharmacology*, University of Michigan, Ann Arbor.	Effects of tobacco smoke and nicotine on the central nervous system (P)
JOHN W. ECKSTEIN, M.D., *Assistant Professor of Internal Medicine*, College of Medicine, State University of Iowa, Iowa City.	Responses of the peripheral veins in man to the intravenous administration of nicotine (P) Foot blood flow responses to smoking in the presence of hyperlipemia and hypertension
HANS L. FALK, PH.D., *Senior Research Associate, Department of Pathology*, University of Southern California School of Medicine, Los Angeles.	Examination of cigarette paper and cigarette smoke condensates for aromatic polycyclic hydrocarbons (C) A compilation of fluorescence spectra of polycyclic aromatic hydrocarbons and closely related compounds which are of interest in the study of air pollutants, and cigarette smoke in relation to lung cancer etiology (C—P) The effects of tobacco smoke condensate

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GRANTEE AND INSTITUTION	PROJECT TITLE
	on the defense mechanisms of the rat in detoxification of polycyclic aromatic hydrocarbons and the competitive inhibition between the polycyclic hydrocarbons in condensate with regard to carcinogenesis
	The physical and chemical properties of mucus under normal conditions and following exposure to aerosol irritants
DANA L. FARNSWORTH, M.D., *Henry K. Oliver Professor of Hygiene and Director of University Health Services*, Harvard University, Cambridge, Mass. (see Heath and McArthur)	Personality and smoking in college graduates: a fifteen-year follow-up study (C)
FRANK C. FERGUSON, JR., M.D., *Chairman, Department of Pharmacology*, Albany Medical College, Albany, N. Y.	Effects of tobacco smoke upon the function of the cardiovascular system in animals and man (C)
RUSSELL S. FISHER, M.D., *Chief Medical Examiner*, State of Maryland; *Professor of Legal Medicine*, University of Maryland Medical School, Baltimore.	Pathologic—anatomic study of cellular changes in human bronchi (C)
B. E. FREEDLANDER, M.D., *Director of Cancer Research*, Mount Zion Hospital and Medical Center, San Francisco, Calif. (deceased, see French)	Experiments on the possible carcinogenic and cocarcinogenic action of tobacco products (C—P)
FREDERICK A. FRENCH, A.B., *Research Associate*, Mount Zion Hospital and Medical Center, San Francisco, Calif. (see Freelander)	Carcinogenicity, cocarcinogenicity and anti-carcinogenicity of dietary factors in relation to pulmonary tumors. Possible interrelationship of tobacco bases and dietary factors. Chemical studies on pyridine bases including niacin analogs
JACK FREUND, M.D., *Assistant Professor of Pharmacology*, Medical College of Virginia, Richmond	Correlation of multitechnical procedures performed on the peripheral circulation of normal individuals in recumbent and erect positions and after exercise before and after sham and actual smoking (C)
	A study of the effects of cigarette smoking on the peripheral circulation of individuals with arteriosclerosis obliterans and other peripheral vascular diseases, utilizing multitechnical procedures (C)
GEORGE O. GEY, M.D., *Director, Tissue Culture Research Laboratory, Department of Surgery*, Johns Hopkins Hospital, Baltimore, Md.	Fellowships for studying the culture of human lung tissue and the effects of known and possible carcinogenic agents upon such tissue
JAMES GORE, M.D., *Chief, Laboratory Service*, Veterans Administration Hospital, West Roxbury, Mass.	Interactions of arterial acid mucopolysaccharides

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GRANTEE AND INSTITUTION	PROJECT TITLE
GERTRUDE Y. GOTTSCHALL, PH.D., *Assistant Professor of Biochemistry, Department of Pathology and Microbiology,* The Rockefeller Institute for Medical Research, New York, N. Y. (see Clarke)	Proteolytic activities of the white blood cells of man and the effect on white blood cell activities of carcinogens, nutrition and other influences (C)
A. CLARK GRIFFIN, PH.D., *Head of Biochemistry Department,* M.D. Anderson Hospital and Tumor Institute, University of Texas Medical Center, Houston.	The effect of exposure to cigarette smoke on the induction of cancer by chemical compounds (C—P)
MORTON I. GROSSMAN, PH.D., M.D., *Associate Clinical Professor of Medicine,* University of California Medical Center, Los Angeles.	The effect of smoking on certain gastric functions (C)
CARL C. GRUHZIT, PH.D., M.D., *Associate in Physiology and Pharmacology,* University of Pennsylvania Graduate School of Medicine, Philadelphia (now Lecturer in Physiology, University of Hong Kong)	Pharmacologic study of nicotine and related alkaloids (C)
H. B. HAAG, M.D., *Professor of Pharmacology,* Medical College of Virginia, Richmond (deceased)	Preparation for publication of a book on the biologic aspects of tobacco and its smoke (C—P)
JOSEPH H. HAFKENSCHIEL, M.D., *Director, Cardiopulmonary Unit,* Lankenau Hospital, Philadelphia, Pa.	Measurement of coronary blood flow, cardiac work and cardiac oxygen and carbohydrate metabolism in normotensive subjects before and after intravenous nicotine and after smoking standard cigarettes (C—P)
RICHARD J. HAVEL, M.D., *Assistant Professor of Medicine,* University of California Medical School, San Francisco.	A study of the effects of smoking and nicotine administration on sympathoadrenal function and fatty acid metabolism
HERBERT R. HAWTHORNE, M.D., *Chairman, Department of Surgery,* University of Pennsylvania Graduate School of Medicine, Philadelphia.	Attempts to induce pulmonary neoplasms in experimental animals by exposure of the tracheobronchial system to tobacco smoke (C)
CLARK W. HEATH, M.D., *Professor of Medicine and Director of Health Services,* Tufts University, Medford, Mass. (see Farnsworth and McArthur)	Personality and smoking in college graduates: a fifteen-year follow-up study (C—P)
PAULINE HEIZER, PH.D., *Research Associate in Cytology and Cytochemistry,* San Francisco Institute of Medical Sciences, San Francisco, Cal. (see Richards)	A comparative study of early histological and DNA changes in the epidermis of two strains of mice (C57 Blacks and Swiss Websters) after daily applications of whole cigarette smoke condensate (alone and combined with croton oil) and the carcinogens 20-methylcholanthrene and 3,4-benzpyrene (C)

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GRANTEE AND INSTITUTION	PROJECT TITLE
LAWRENCE L. HESTER, JR., M.D., *Professor and Chairman, Department of Obstetrics and Gynecology,* Medical College of South Carolina, Charleston.	The relationship of the use of tobacco products to the outcome of pregnancy (C)
EBBE CURTIS HOFF, PH.D., M.D., *Professor and Chairman, Department of Neurological Science,* Medical College of Virginia, Richmond.	Cerebral autonomic changes produced by tobacco smoke, nicotine or cotinine, a metabolite of nicotine
RUSSELL L. HOLMAN, M.D., *Professor and Head, Department of Pathology,* Louisiana State University School of Medicine, New Orleans. (deceased, see McGill and Strong)	Pathologic—anatomic study of cellular changes in human bronchi (C) The influence of tobacco smoking on acute myocardial infarction (C)
F. HOMBURGER, M.D., *President,* Bio-Research Institute, Inc., Cambridge, Mass.	Studies on carcinogenesis and the bioassay of carcinogenic agents (P) Comparative studies of effects of various tobacco smoke condensates on skins of mice
ROBERT W. HULL, PH.D., *Assistant Professor of Zoology,* Northwestern University, Evanston, Ill.	Photodynamic activation of carcinogenic hydrocarbons: (a) standardization of assay techniques utilizing protozoa; (b) investigation of the mechanisms of activation and response to aromatic carcinogens by protozoa
JERRY HART JACOBSON, M.D., *Director of Electrophysiology,* New York Eye and Ear Infirmary, New York, N. Y.	A comparison of electroretinography as a means of evaluating the effect of vasoconstrictor drugs upon cerebral and retinal circulation with other techniques for this determination (C)
JULIUS H. JACOBSON II, M.D., *Associate Professor of Surgery and Director of Surgical Research,* College of Medicine, University of Vermont, Burlington.	Lung homotransplantation (C)
MURRAY E. JARVIK, PH.D., *Associate Professor of Pharmacology,* Albert Einstein College of Medicine, Bronx, N. Y.	Pilot study of habituation to nicotine by means of rhesus monkeys
ANDREW A. KANDUTSCH, PH.D., *Staff Scientist,* Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Me.	To determine to what extent tobacco 'tar' mimics the action of carcinogenic hydrocarbons in the skin and other tissues (C)
ANCEL KEYS, PH.D., *Professor of Physiological Hygiene and Director, Laboratory of Physiological Hygiene,* University of Minnesota School of Public Health, Minneapolis.	Characteristics of men, including smoking, in populations differing in the incidence of coronary heart disease (C—P)
JOSEPH B. KIRSNER, M.D., *Professor of Medicine,* University of Chicago School of Medicine, Chicago, Ill.	The effect of tobacco smoking upon basal gastric secretions in man (C)

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GRANTEE AND INSTITUTION	PROJECT TITLE
KENNETH P. KNUDTSON, M.D., *Assistant Chief, Laboratory Service,* Veterans Administration Hospital, Seattle, Wash.; *Professor of Pathology,* University of Washington Medical School, Seattle.	Pathologic—anatomic study of cellular changes in human bronchi (C—P)
ALVIN I. KOSAK, PH.D., *Associate Professor of Chemistry,* Washington Square College, New York University, New York, N. Y.	The isolation and identification of certain lower-boiling components of cigarette smoke (C)
ROBERT A. KUHN, M.D., *Associate Professor of Neurology and Neurosurgery,* New York Medical College, New York, N. Y.	Possible effects of tobacco upon cerebral circulation
MARVIN KUSCHNER, M.D., *Professor of Pathology,* New York University College of Medicine; *Director of Pathology,* Bellevue Hospital, New York, N. Y.	Pathologic—anatomic study of cellular changes in human bronchi (C)
THOMAS C. LAIPPLY, M.D., *Associate Professor of Pathology,* Northwestern University Medical School, Chicago, Ill.	Pathologic—anatomic study of cellular changes in human bronchi (C)
PAUL S. LARSON, PH.D., *Professor of Pharmacology;* Medical College of Virginia, Richmond. (see McKennis)	Enzymatic transformations of nicotine and related compounds (P) The possible effect of tobacco smoke and nicotine on ascorbic acid metabolism
GUSTAVE A. LAURENZI, M.D., *Assistant Professor of Medicine,* Seton Hall College of Medicine, Jersey City, N. J.	Studies in bronchitis: a correlated investigation of (a) the effect of smoking on the bacteriology of the respiratory tract of humans, and (b) the effect of cigarette smoke and sulfur dioxide (air pollutant) on the clearing of bacteria from the respiratory tracts of small animals (mice, rats)
CECILIE LEUCHTENBERGER, PH.D., *Senior Biologist and Cytochemist,* Sias Memorial Laboratories, Brooks Hospital, Brookline, Mass. (In residence at Institut für Allgemeine Botanik, Eidgenossische Technische Hochschule, Zurich, Switzerland)	A correlated histological, cytological and cytochemical study of the tracheobronchial tree of mice exposed to cigarette smoke (P)
ESTEN O. LINDSETH, M.D., *Surgical Service,* Veterans Administration Hospital, Minneapolis, Minn.	Measurement of the differential blood flow in the mammalian lung during the acute period of smoke inhalation, using the open chest animal and the method and principle of gamma emitting radioactive graded microspheres
ROBERT H. LINNELL, PH.D., *Associate Professor of Chemistry,* University of Vermont, Burlington (now at Scott Research Laboratories, Perkasie, Pa.)	The oxidation of nicotine by gaseous oxygen: mechanism, products and kinetics (C—P) The autoxidation of nicotine

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GRANTEE AND INSTITUTION	PROJECT TITLE
J. P. LONG, PH.D., *Associate Professor of Pharmacology*, State University of Iowa, College of Medicine, Iowa City.	Cardiovascular effects of nicotine
DAVID E. MANN, JR., PH.D., *Associate Professor of Pharmacology* Temple University School of Pharmacy, Philadelphia, Pa.	Effect of tobacco smoke and tobacco residues on methylcholanthrene-induced skin carcinogenesis in mice (C)
CHRISTOPHER M. MARTIN, M.D., *Assistant Professor of Medicine and Director, Division of Infectious Diseases*, Seton Hall College of Medicine, Jersey City, N. J.	Possible interactions of viruses and substances in tobacco smoke condensate (P)
CHARLES C. McARTHUR, PH.D., *Psychologist to the University Health Services*, Harvard University, Cambridge, Mass. (see Heath and Farnsworth)	Social and personal determinants of smoking behavior (C—P) The social mediation of smoking behavior (C)
CHARLES B. McCANTS, PH.D., *Associate Professor of Soils*, School of Agriculture, North Carolina State College, Raleigh.	Arsenic content of soils and absorption by the tobacco plant (C—P)
HENRY C. McGILL, JR., M.D., *Acting Head, Department of Pathology*, Louisiana State University School of Medicine New Orleans. (see Holman and Strong)	The effects of environmental factors on development of atherosclerosis as revealed by autopsy of accident victims
FORDE A. McIVER, M.D., *Assistant Professor of Pathology*, Medical College of South Carolina, Charleston.	Environmetal factors and pulmonary disease. I. Asbestos dust
MURRY B. McKEE, M.D., *Associate Professor of Medicine*, Medical College of South Carolina, Charleston.	Study of lung function in smokers and nonsmokers (C—P)
HERBERT McKENNIS, JR., Ph.D., *Professor of Pharmacology*, Medical College of Virginia, Richmond (see Larson)	Enzymatic transformations of nicotine and related compounds
VICTOR A. McKUSICK, M.D., *Associate Professor of Epidemiology and Chief, Division of Medical Genetics*, Johns Hopkins University School of Medicine, Baltimore, Md.	A combined genetic, physiologic, clinical and epidemiologic study of Buerger's disease
JAMES G. MILLER, M.D., PH.D., *Professor of Psychiatry and Psychology, and Director, Mental Health Research Institute*, University of Michigan, Ann Arbor.	The behavioral effects of smoking under stress (C)
HUGH MONTGOMERY, M.D., *Associate Professor of Medicine*, University of Pennsylvania Medical School, Philadelphia.	Influence of tobacco smoking on the blood flow of skin and of muscles of extremities in sympathectomized and unsympathectomized subjects (C) Influence of nicotine (i.v.) and tobacco smoking on blood flow in human skin and skeletal muscle (C—P)

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GRANTEE AND INSTITUTION	PROJECT TITLE
P. O'B. MONTGOMERY, JR., M.D., *Associate Professor of Pathology*, University of Texas, Southwestern Medical School, Dallas.	Investigation of the role of the nucleolus in the normal and the malignant cell (P)
GEORGE E. MOORE, PH.D., M.D., *Director*, Roswell Park Memorial Institute, Buffalo, N. Y. (see Bock)	An investigation of the physiological effects of direct inhalation of tobacco smoke by laboratory animals and the study of the biological response of laboratory animals to continuous ingestion of diet-tobacco product mixtures (C)
HURLEY LEE MOTLEY, M.D., *Professor of Medicine and Director, Cardio-Respiratory Laboratory*, University of Southern California School of Medicine, Los Angeles.	A study of the effects of smoking on pulmonary function (C—P)
WILLIAM S. MURRAY, SC.D., *Research Associate*, Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Me.	The production of genetically controlled animals and tumors for use in experimental research on tobacco in relation to health (C)
	Studies of the mammary tumor-promoting qualities of a virus-like principle, under varying hormonal and aging conditions
DONALD M. PACE, PH.D., *Professor of Physiology and Director, Institute for Cellular Research*, University of Nebraska, Lincoln.	Fellowship for training in tissue culture techniques (C)
	Study of the effects of tobacco smoke constituents on various strains of tissue cells cultivated *in vitro* (P)
EDWARD W. PELIKAN, M.D., *Associate Professor of Pharmacology and Experimental Therapeutics*, Boston University School of Medicine, Boston, Mass.	A study of structure-activity relationships among drugs which affect nicotine-sensitive physiological mechanisms (P)
OTAKAR J. POLLAK, M.D., PH.D., *Executive Director*, Dover Medical Research Center, Inc., Dover, Del.	Possible effect of tobacco derivatives on arterial and myocardial tissue cultures (P)
C. M. POMERAT, PH.D., *Director of Biological Research*, Pasadena Foundation for Medical Research, Pasadena, Cal.	Fellowships for studying the culture of human lung tissue and the effects of known and possible carcinogenic agents upon such tissue (C—P)
H. R. PRATT-THOMAS, M.D., *Dean and Professor of Pathology*, Medical College of South Carolina, Charleston.	Pathologic—anatomic study of cellular changes in human bronchi (C—P)
	Application of a new bioassay technique in examination of cigarette smoke condensates for possible carcinogens (C—P)
	Carcinogenesis in the laboratory animal: a comparison of species response to standardized sites of application

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GRANTEE AND INSTITUTION	PROJECT TITLE
WALTER REDISCH, M.D., New York University Research Service, Goldwater Memorial Hospital, Welfare Island, New York, N. Y. (see Sulzberger)	Vascular responses to tobacco smoking in patients with vascular disease
HOBART A. REIMANN, M.D., *Professor of Medicine*, Hahnemann Medical College and Hospital, Philadelphia, Pa.	The possible effect of tobacco or nicotine in periodic disorders, a newly-recognized syndrome (C—P)
VICTOR RICHARDS, M.D., *Professor of Surgery and Executive Head, Department of Surgery*, Stanford University School of Medicine, San Francisco, Cal. (see Heizer)	A comparative study of the effects of whole and fractional extracts of cigarette smoke and those of known carcinogens on (1) the cytology and nuclear DNA content of epidermis in various strains of mice and/or (2) the cytology and nuclear DNA content of lung and epithelium of the bronchial tree of mice and hamsters (C)
R. H. RIGDON, M.D., *Professor of Pathology and Director, Laboratory of Experimental Pathology*, University of Texas Medical Branch, Galveston.	Effects of tobacco smoke condensate on the respiratory tract and other tissues of the duck (C—P)
SYDNEY C. RITTENBERG, PH.D., *Professor of Bacteriology*, University of Southern California, Los Angeles.	The bacterial degradation of nicotine and related compounds. The objective of the project is the elucidation of the intermediary metabolism of nicotine oxidation (C—P)
HUNSON B. ROE, M.D., *Associate Professor of Surgery, Department of Surgery*, University of California School of Medicine, San Francisco.	Study of the action of negatively charged ions on tracheobronchial ciliary action in the human patient
BENJAMIN A. RUBIN, PH.D., *Assistant Professor of Public Health and Preventive Medicine*, Baylor University College of Medicine, Houston, Texas. (now at Wyeth Laboratories, Philadelphia, Pa.)	An evaluation of the phenomenon of tumor growth enhancement as an assay for carcinogens among the polycyclic hydrocarbons and related compounds (C)
WILLIAM O. RUSSELL M.D., *Pathologist-in-chief*, M.D. Anderson Hospital and Tumor Institute, University of Texas Medical Center, Houston.	Pathologic—anatomic study of cellular changes in human bronchi (C)
PETER F. SALISBURY, M.D., *Head, Intensive Treatment Center*, Saint Joseph Hospital, Burbank, Cal.	Influence of nicotine and catecholamines upon coronary vasomotor tonus in normal and atherosclerotic dogs
PAUL D. SALTMAN, PH.D., *Assistant Professor of Biochemistry*, University of Southern California School of Medicine, Los Angeles.	The enzymatic mechanism for the dark fixation of CO_2 by tobacco (C—P) Some aspects of amino acid metabolism in tobacco leaves (C)
ALVIN R. SCHMIDT, PH.D., *Director of Counseling*, Tufts University, Medford, Mass.	Study of attitudes toward, as well as extent, type and history of, tobacco smoking in a young college population. Study of some of the relationships of smoking and nonsmoking to

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GRANTEE AND INSTITUTION	PROJECT TITLE
	family history, type of secondary schooling, academic interests, academic achievement, and social relationships characteristics (C)
ISAAC SCHOUR, D.D.S., PH.D., D.SC., *Professor of Histology and Embryology and Dean*, University of Illinois College of Dentistry, Chicago.	Histologic changes in the oral, pharyngeal and nasal tissues of experimental animals subjected to tobacco smoke (C—P)
MAURICE S. SEGAL, M.D., *Clinical Professor of Medicine*, Tufts University School of Medicine, Boston, Mass.; *Director, Department of Inhalation Therapy*, Boston City Hospital.	Effects of cigarette smoking on lung function in normal subjects and patients with certain respiratory disease conditions (C—P) Relationship of cigarette smoking to chronic (obstructive) pulmonary emphysema (C)
CARL C. SELTZER, PH.D., *Research Fellow in Physical Anthropology*, Harvard University, Cambridge, Mass.	Morphology and smoking in college graduates: a fifteen-year follow-up study (P) Harvard-Johns Hopkins study of body form as related to smoking, and the precursors of hypertension and coronary artery disease.
CHARLES E. SHERWOOD, M.D., *Assistant Professor of Radiology*, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.	Investigation into the natural history of carcinoma of the lung with particular reference to the radiographic appearance of such processes, the earliest manifestation of cancer on chest X-ray photographs and the tabulation of the relationship of smoking habits and occupation with the incidence of lung cancer (C—P)
DAVID L. SIMON, M.D., *Instructor in Medicine and Fellow in Cardiovascular Research*, University of Cincinnati College of Medicine and Cardiac Laboratory, Cincinnati General Hospital, Cincinnati, O.	The effects of chewing tobacco on the cardiovascular system of man (C—P) The effects of pipe smoking and cigar smoking on the cardiovascular system of man (C—P)
T. M. SONNEBORN, PH.D., *Distinguished Service Professor of Zoology*, Indiana University, Bloomington.	Checking and extending the Stephano *Paramecium* test for carcinogenicity (C)
SAM SOROF, PH.D., *Research Associate*, The Institute for Cancer Research and Lankenau Hospital Research Institute, Philadelphia, Pa.	Chemical and physical studies of the tissue proteins involved in chemical carcinogenesis (C—P)
FREDRICK J. STARE, PH.D., *Professor of Nutrition*, Harvard School of Public Health, Boston, Mass.	Experimental studies of cancer utilizing a new technique to see if various 'tars' extracted from tobacco may incite the formation of lung tumors (C)
JACK P. STRONG, M.D., *Associate Professor of Pathology*, Louisiana State University School of Medicine, New Orleans (see Holman and McGill)	The effects of environmental factors on development of atherosclerosis as revealed by autopsy of accident victims

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GRANTEE AND INSTITUTION	PROJECT TITLE
MARION B. SULZBERGER, M.D., *Professor and Chairman, Department of Dermatology and Syphilology,* New York University-Bellevue Medical Center, New York, N. Y. (retired, see Redisch)	Investigation of the effects of tobacco on the human vascular system, based on the fact that certain tobacco effects are due to allergic susceptibility of specific individuals rather than to obligatorily toxic products in tobacco smoke, and that patients with occlusive vascular diseases respond differently than healthy smokers (P)
RENATO TAGIURI, PH.D., *Associate Professor of Psychology, Graduate School of Business Administration,* Harvard University, Boston, Mass.	Critical review of literature on psychology of smoking
CAROLINE BEDELL THOMAS, M.D., *Associate Professor of Medicine,* Johns Hopkins University School of Medicine, Baltimore, Md.	The significance of different individual patterns of circulatory response to cigarette smoking (P) Studies of genetic differences between smokers and nonsmokers (P) Studies of psychological differences between smokers and nonsmokers as shown by comparison of figure drawings (P)
TISSUE CULTURE ASSOCIATION	To assist in establishing of summer training course in tissue culture techniques at University of Colorado Medical School, Denver, Colo. (C)
JANET TRAVELL, M.D., *Associate Professor of Clinical Pharmacology,* Cornell University Medical College, New York, N. Y.	Effects of nicotine in the rabbit with experimental coronary atherosclerosis (C—P)
E. D. WARNER, M.D., *Professor of Pathology,* State University of Iowa College of Medicine, Iowa City.	Pathologic—anatomic study of cellular changes in human bronchi (C—P) Correlation of bronchial epithelial changes with comparable changes in other organs—a pathologic-anatomic study (C—P)
SHIELDS WARREN, M.D., *Director of Laboratories, Cancer Research Institute,* New England Deaconess Hospital, Boston, Mass.	The pattern of metastasis of carcinoma of the lung in man Histopathology of human lung cancer
RICHARD L. WECHSLER, M.D., *Clinical Physiologist,* Montefiore Hospital Institute of Research, Pittsburgh, Pa.	Effect of cigarette smoking on cerebral blood flow, cerebral metabolism, blood gases, blood pH, arterial pulse pressure curves, electrocardiograms, and electroencephalograms (C)
RUSSELL W. WELLER, M.D., *Pathologist,* Memorial Hospital of Chester County, West Chester, Pa.; *Associate Professor of Pathology,* Hahnemann Medical College, Philadelphia, Pa.	Pathologic—anatomic study of cellular changes in human bronchi (C) A selected, extended and detailed study of human bronchial mucosa

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GRANTEE AND INSTITUTION	PROJECT TITLE
SIMON H. WENDER, PH.D., *Research Professor of Chemistry,* University of Oklahoma Research Institute, Norman.	A qualitative and quantitative study of the individual polyphenol content of cigarette tobacco and the smoke and 'tars' resulting from cigarette smoking, and also study of the fate of these compounds in the animal respiratory system (C—P)
DUANE G. WENZEL, PH.D., *Professor of Pharmacology,* School of Pharmacy, University of Kansas, Lawrence.	The determination of the chronic effects of orally administered nicotine on serum cholesterol and phospholipids; the electrocardiographic response to ergonovine; and the vascular pathology of cholesterol-fed rabbits (C—P)
FREDERICK E. WHISKIN, M.D., C.M., *Director, Division of Health and Personality Equilibrium,* The Age Center of New England, Inc., Boston, Mass. (see Dibner)	Pilot study of smoking habits of Age Center members (C)
ROGER J. WILLIAMS, PH.D., *Professor of Chemistry and Director, Clayton Foundation Biochemical Institute,* The University of Texas, Austin.	An investigation of biochemical factors associated with susceptibility to lung cancer
J. EDWIN WOOD, M.D., *Professor of Medicine,* Medical College of Georgia, Augusta.	The effect of prolonged inhalation of tobacco smoke and of prolonged abstinence from the use of tobacco on the peripheral vascular response to acute inhalation of tobacco smoke in man (C—P)
SUMNER WOOD, JR., M.D., *Assistant Professor of Pathology, Department of Pathology,* Johns Hopkins University, Baltimore, Md.	Evaluation of etiologic factors, such as occupational hazards and habits, and pathologic peculiarities in the long-term survival of patients following resection for bronchogenic carcinoma
JOHN P. WYATT, M.D., *Professor of Pathology,* St. Louis University School of Medicine, St. Louis, Mo.	An investigation into the nature of the pigmentary lesions in centrilobular emphysema (C)

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